HINDUSTAN ANTIBIOTICS

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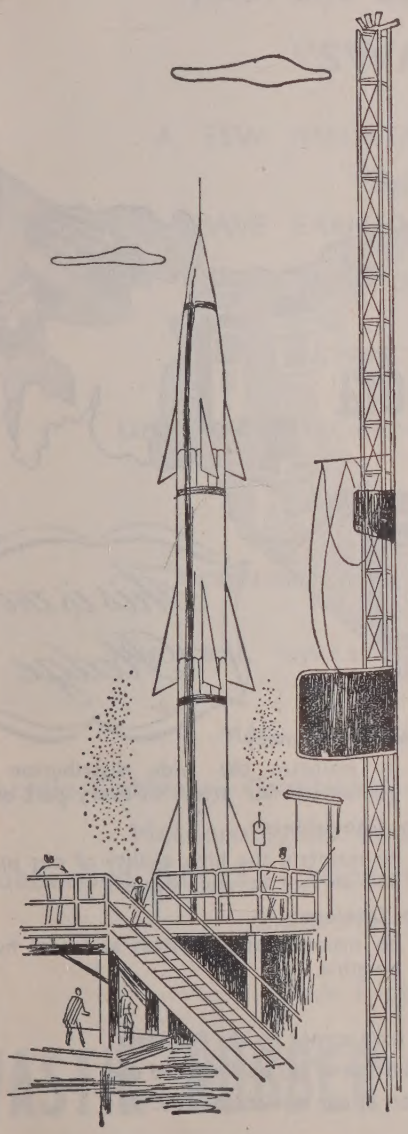

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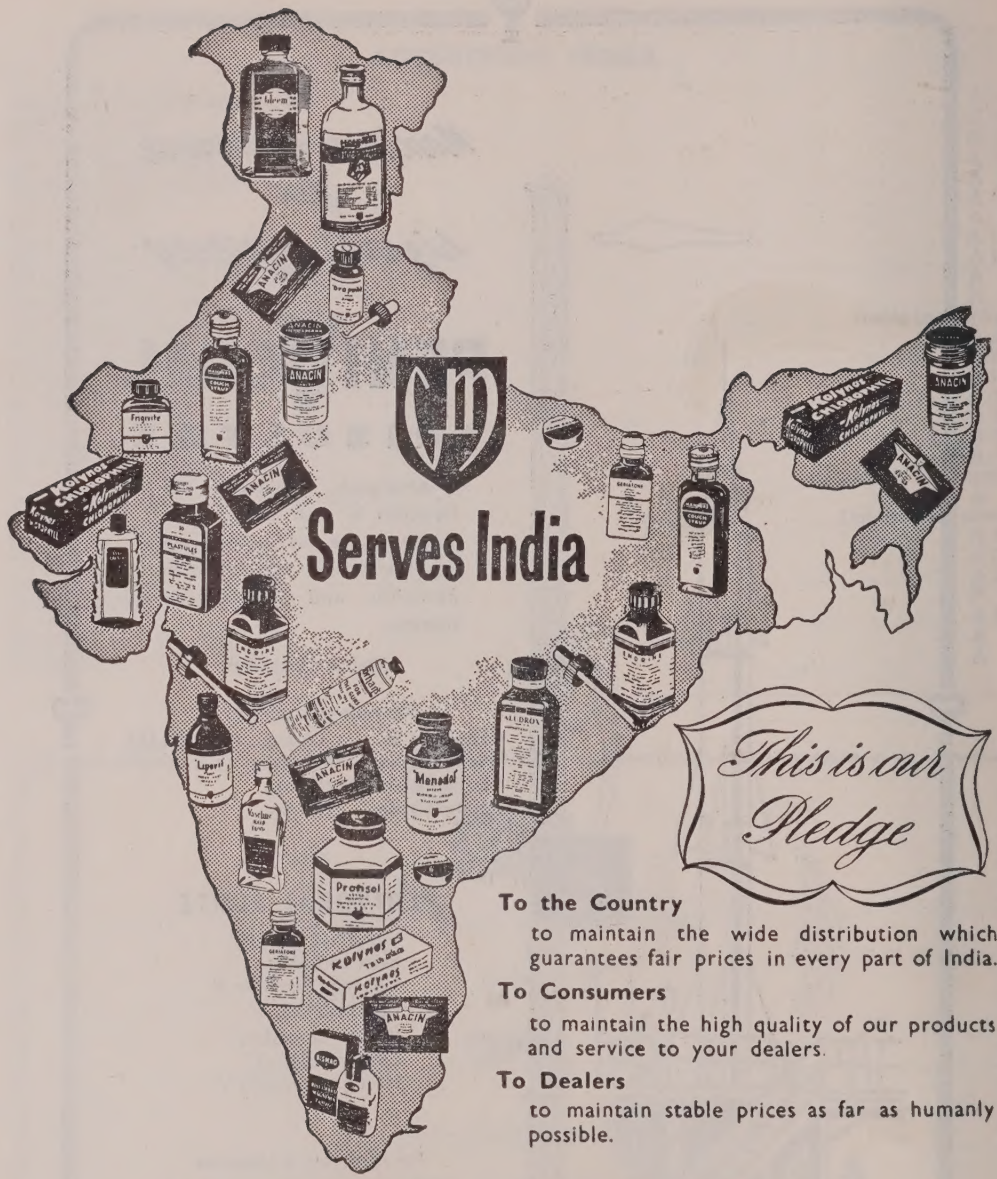

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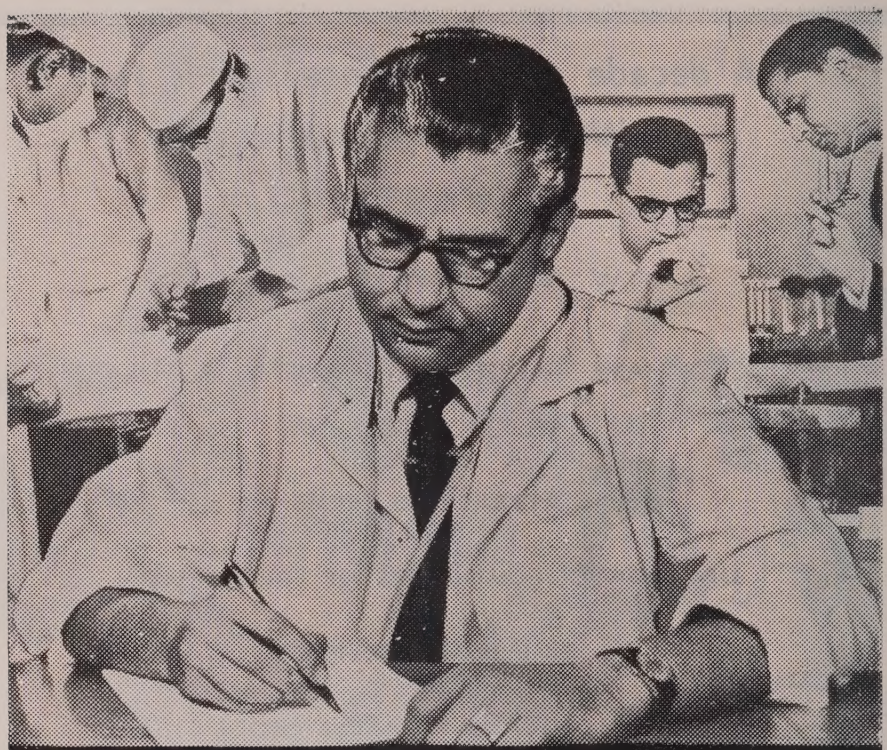

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2nd Year....

With this issue, *Hindustan Antibiotics Bulletin*, enters its second year of publication. As befitting the house journal of a national undertaking, the inaugural number was issued on a day of the nation's re-dedication to its people's welfare and progress — 15th August, 1958.

The publication of a journal designed as a medium for fostering better understanding between those engaged in the production and supply of vital drugs and those who use them through dissemination of impartial and authoritative information, obviously entails a good deal of responsibility. Hence, it was with a sense of humility that we placed the first issue in the hands of the scientific and non-scientific public. It is gratifying that our humble effort has been well received all over the world, and judged from the letters of appreciation and encouragement we have received, the journal can embark on the second year with a certain amount of satisfaction.

To all the contributors who placed themselves at our disposal, to the printers and advertisers who extended a co-operative and helping hand, we express our thanks. To the learned societies, institutions and journals who have sent in exchange, valuable scientific and technical publications, and reviewed, abstracted and indexed the *Bulletin*, we are most grateful.

As the journal goes into the second volume we hope to include original articles and other new features in addition to the regular reviews and information sections, so that it may reflect the variety of subjects with which an undertaking such as Hindustan Antibiotics is concerned. We feel assured of the continued support and sympathy of all who have encouraged us and we hope to make many more friends and well-wishers.

EDITORS.

Combined Antibiotic Therapy

Combinations of antibiotics for therapy against human diseases have been widely used. Discovery of a large number of new antibiotics with different antimicrobial spectra, has enabled detailed studies on the combined effects of antibiotics *in vitro* and *in vivo*. Combinations are often used (or misused) when bacteriological data on the disease inciting organism are not available and the patient has to be treated immediately. However, combined therapy has its own advantage as in cases of mixed infection by bacteria, and bacteria and fungi, sensitive to different antibiotics, or in those cases where sufficient antibiotic level cannot be attained by the use of one antibiotic alone. Further, in the case of combined antibiotic therapy, the emergence of resistant organisms is delayed.

When two antibiotics are used as combination in controlling disease incited by a homogenous bacterial population, the effects may be one of the following, as pointed out by Jawetz and Gunnison : (a) *Indifference*—where the combined action is no greater than that of the more potent one when used alone ; (b) *addition*—the combined action is equivalent to the sum of activity of each drug when used alone ; (c) *synergism*—combined action is greater than the sum of activity of both ; (d) *antagonism*—the combined action is less than that of the more effective component when used alone. Jawetz and Gunnison further divided the antibiotics that are in use into two main groups, one comprising the more bactericidal types like penicillin, streptomycin, bacitracin, etc, and the second group including the bacteriostatic ones like tetracyclines, chloramphenicol, and erythromycin.

GROUP I :	Penicillin	
	Streptomycin	
	Bacitracin	
	Polymyxin B	
	Neomycin	
	Oleandomycin	
GROUP II :	Chlortetracycline	Tetracyclines
	Oxytetracycline	
	Tetracycline	
	Chloramphenicol	
	Erythromycin	
	Novobiocin	

In therapeutic use, combining members of Group I was considered safe. They would be synergistic or indifferent and never antagonistic. Combining members of Group II would be additive or indifferent and never synergistic or antagonistic. Combinations of Groups I and II might produce antagonism and are rarely synergistic.

In 1943, Ungar was the first to show the synergistic action of penicillin and sulfapyridine, and subsequent clinical experiences with this combination substantiated the original observations. In 1947 Klein and Kimmelman showed synergistic action *in vitro* of penicillin and streptomycin and, this antibiotic pair has been found effective against micrococcic bacterial endocarditis resistant to enormous doses of penicillin. Antibiotic literature is full of reports of cases treated with various antibiotic combinations. Results of the use of penicillin-novobiocin, tetracyclines-oleandomycin, penicillin-streptomycin, tetracyclines-nystatin, tetracycline-novobiocin and others have been described, preference being given by each investigator to some particular antibiotic. In the case of oleandomycin and penicillin, they were even chemically combined as a salt termed "Oleandopen" and shown to have an additive activity.

The concepts synergism, antagonism in combined antibiotic therapy as propounded by Jawetz *et al* have become generally accepted by most of the investigators, but some of the aspects of actual working have often been overlooked. For instance, the influence of bacterial resistance has not been taken into account. If resistance to antibiotics is considered to arise from spontaneous mutations, the number of bacteria present at the time of treatment becomes important. Hence, when there is a large bacterial population, resistant organisms may be present and get selected out by the drug, whereas, in small populations these may be absent.

It is evident that the size of the inoculum influences the final results of antibiotic therapy. Using *Klebsiella pneumoniae*, Julius and Gaikhorst studied the combined effects of streptomycin and chloramphenicol. When the inoculum potential was low, streptomycin alone was superior to the combined effects of streptomycin and chloramphenicol. This combination would be branded as antagonistic since chloramphenicol reduces the efficacy of streptomycin. However, when the initial inoculum was high, use of streptomycin alone resulted in the rapid development of streptomycin-resistant strains and consequent death of the inoculated animals. Chloramphenicol by itself could not suppress development of resistant strains, but in combination, the resistant strains were suppressed and the action was almost synergistic. It is evident that in this case synergism or antagonism is determined not by the combination of the drugs alone, but is influenced by the amount of initial bacterial inoculum.

Problems in the Extraction of Penicillin

S. R. SEN

The separation and purification of antibiotics from the culture fluids involve a series of critically controlled chemical and physico-chemical operations. Production on a commercial scale consists in starting from an impure biological product obtained by fermentation and ultimately arriving at a chemical with the highest degree of purity having physical properties within strictly set standards and obtaining, at the same time, maximum practicable recovery of the product estimated to be present in the fermented broth. To achieve this object extraction, crystallisation and recrystallisation operations have to be carried out. Ninety per cent of the solids content of the filtered fermented broth are impurities which must be eliminated in order to obtain penicillin crystals of 98 to 99 per cent purity. These impurities interfere with the efficient recovery of the product causing losses and necessitating elaborate handling. The process of extraction has to be so devised as to effect the removal of impurities and increase the concentration of the product in solution from which crystallisation of the solid is practicable. It, therefore, serves as a link between the biochemical process of elaboration of the antibiotic and the chemical process of isolation of the crystals.

Number of variations are feasible in the chemical processes for recovering an antibiotic from its culture fluid. Only a few of them, however, attain commercial acceptance in view of their specific advantages, the percentage recovery obtainable by a particular process being the foremost consideration. Considerations of cost of the chemicals required for processing as well as the hazards in their large scale handling are also of importance. In general, the recovery processes for antibiotics can be grouped under three heads: Adsorption, solvent extraction and precipitation methods. Often a combination of two or more of these methods are applied to achieve the best results. Carbon adsorption and ion-exchange applications come under the first category. Recovery by these methods are comparatively low and are taken recourse to when it is not possible to recover the product by any other method. Solvent extraction methods involve transfer of the product from one phase to the other thereby eliminating impurities and increasing the concentration in the solvent phase. Precipitation methods are means of isolating the product from its solution as a complex salt and thereafter breaking up the complex to obtain the pure product.

Penicillin is extracted from the fermented broth by the solvent extraction process. In broad general outline the process consists in transferring penicillin from the water solution into an organic solvent phase under acidic conditions. The impurities are partially removed. The penicillin in solution is subjected to another transfer from the solvent to the water phase in the form of its salt. This repetitive process of extraction from solvent phase to water and *vice versa* is carried on in order to obtain a concentration and purity, which makes it possible subsequently to crystallise penicillin by simple operations. In practice two or four extraction steps are employed depending on the conditions prevailing in a particular plant. The quality of the broth and the equipment facilities available determine the yields obtainable by these

two methods. Choice falls naturally on the method giving higher yields.

The transfer operations create certain problems when translated into practice. Most important of these is the inactivation of penicillin. The acid pH required for the efficient transfer of penicillin into the solvent leads to rapid destruction of penicillin in aqueous solutions. In fact, at room temperature the half-life of penicillin in aqueous solution at pH 2 is 18 minutes. Although the rate of inactivation is less at higher pH values, the transfer becomes less efficient. Therefore, to maintain optimum conditions it is essential that the extraction is completed very rapidly. Extraction operation is further complicated by the phenomenon of emulsification. The fermented broth, containing mould metabolites when mixed with the solvent under the acidic condition of extraction, forms emulsion. This is undesirable in that it prevents separation of penicillin-rich solvent phase. Moreover, prolonged and intimate contact of penicillin with the acid accelerates decomposition. This problem is solved by the addition of a surface active agent to the extent of about 0.01 per cent to the broth. It is interesting that wetting agents having emulsifying action are useful in the de-emulsification in this system under the conditions prevailing therein. Again, proteinaceous solids separate out during the process of extraction which interfere with the mixing and separation of the broth and solvent. These solids must be removed continuously in order to facilitate transfer.

The factors controlling the theoretical efficiency of transfer of penicillin from broth to the solvent phase are the distribution coefficient of penicillin between solvent and water at pH 2 and the volumetric ratio of solvent to water. It is obvious, that one stage of mixing and separation will not effect complete transfer unless the distribution is extremely favourable. In the system butyl acetate-water-penicillin a single stage extraction with a solvent to water ratio of 1:4 will give a theoretical efficiency of 83 per cent. A second stage of extraction will bring up the recovery figure to 96.9 per cent, a third stage will theoretically yield 99.3 per cent, a fourth stage 99.87 per cent and so on. This shows that in order to obtain maximum transfer at least three successive stages of mixing and separation are necessary. The process is further improved by employing counter-current extraction. In this system the feed broth solution enters at the end opposite to that of the solvent and the flow of the two phases are one against the other. Thus, the fresh solvent meets partially stripped broth and the enriched outgoing solvents meet the incoming rich broth. The smaller concentration gradients in the stages, therefore, bring about equilibrium conditions quicker. Further, a smaller quantity of solvent is used, thereby attaining greater enrichment.

The foregoing discussion indicates that successful industrial application of penicillin extraction calls for multi-stage counter-current operations with shortest possible time of contact for mixing of phases, rapid separation and effective removal of solids. These particulars should, therefore, be incorporated into the machine selected for the operation. An additional factor is corrosion at the low pH of operation. This can be taken care of by selecting the proper material of construction which usually is molybdenum-stabilized stainless steel.

Rapid technological developments in equipment design met the challenge of this process adequately and today several types of extractors are available which accomplish the transfer of penicillin from the broth to the solvent phase with an efficiency amazingly close to the theoretical.

These equipments must necessarily be of the centrifugal type which would effect very rapid separation, and mixing of the phases is also done centrifugally. Column extractors need longer time of contact for approaching equilibrium conditions and are

therefore of little use in the process. The centrifugal separators develop a relative centrifugal force of the order of 5,000 times gravity or more which is adequate to effect satisfactory separation of two phases having a specific gravity difference as low as 0.02.

The Sharples and DeLaval models of centrifugal extractors are one stage extraction machines. Three stage operation is carried out using three machines with intermediate centrifugal pump mixers. In the DeLaval machine closely spaced set of stationary discs are arranged inside the rotating bowl to increase the speed of separation. The bowl contains adequate space to hold the solids separating out during processing. Models incorporating a device for automatic removal of the accumulated sludge have also been developed, in which as soon as a certain amount of solids separate out the feed is cut-off and a jet of water ejects the sludge out of the machine. Normal operation is continued after discharge of the sludge. This is of definite advantage in that it prevents the tapering off of extraction efficiency due to solid accumulation. Very large capacity machines handling upto 25,000 litres per hour are available. The Luwesta extractor is a similar type of centrifugal separator with discs but with the added feature of having three counter-current stages built-in. Mixing is done inside the machine in small discs with volute shaped passage, utilizing the centripetal force created in the liquid by the rotation of the bowl. One pass through the machine, therefore, effects a three-stage counter-current mixing and separation.

The Podbielniak extractor is a centrifugal machine with strikingly different features. The rotor consists of a spiral with a rectangular cross section with perforations. The light liquid travels from the periphery to the centre through the spiral path whereas the heavy liquid flows in the opposite direction. The perforations cause intermixing and extraction equivalent to eight theoretical stages is achieved. One particular model of Podbielniak extractor handles unfiltered whole broth. This has proved to be more suited to handling chloramphenicol broth than that of penicillin. Machines having very high throughout capacity of the order of 100,000 litres per hour have been developed. The manufacturers plan to raise this to 200,000 litres per hour in the near future.

It is a fact that the problems in recovering a fermentation product like penicillin have diminished over the past few years due to the advances in fermentation technology. High concentration of a relatively purer product at the end of fermentation, has been achieved. This has made possible higher yields and better quality products with lesser number of processing operations. It is not correct to view extraction processes from the purely chemical standpoint. It must be admitted that the end products of fermentation and the relative purity of the culture fluid will determine the success or otherwise of the extraction process. A high assay of the fermented broth may not necessarily bring about larger output of good quality product. In other words, any effort towards developing the fermentation process must take into account the problems and difficulties likely to be encountered in the separation and purification stages. This alone will make it possible to obtain the final product at the lowest possible cost.

Research Notes

PRELIMINARY NOTE ON S—39, AN ANTIFUNGAL ANTIBIOTIC

In a routine soil screening programme a sample from Darjeeling yielded a species of *Streptomyces*, tentatively identified as belonging to the section of Spira of Pridham *et al*[1], showing strong antifungal properties. The species is considered nearer to *S. albus* than to *S. cacaoi* in spite of some morphological similarities to the latter. *S. cacaoi* has been reported to be only a plant pathogen[2] and Cacaomycetin which it produces is both antibacterial and antifungal,[3] while the species in question produces an antibiotic active exclusively against filamentous fungi and yeast.

Production of the antibiotic in the usual soyabean-dextrose-sodium chloride medium reached a maximum in 96 hrs. giving 250 to 400 *Candida* units per ml. The antibiotic was also produced in other media like glycerol-ammonium sulphate, glucose-ammonium sulphate, and Czapeks, but best production was in soyabean medium. The antibiotic in solution was stable for 4 hr. at 50°, for 1 hr. at 100° and lost 60 per cent activity when autoclaved for 15 min. at 15 lbs. It was active against most of the filamentous fungi tested including *Eremothecium ashbyii*, *Penicillium chrysogenum*, *Aspergillus nidulans*, *Trichothecium roseum*, *Cephalosporium salmosynnematum*, *Fusarium* spp, and *Penicillium herquei*. It was also active against yeasts including *Candida albicans* which was used as a test organism for all bioassays.

The fermentation broth was filtered through Hyflo Supercel and the clear filtrate concentrated to a small volume at 50° under reduced pressure and the concentrate extracted with light petroleum (B.P. 40-60°). The extracted broth was acidified to pH 3 and immediately extracted with ethyl acetate, the extract washed with water, dried and the solvent removed to give an oil showing activity against *C. albicans*. The active oil was chromatographed on a mixture of alumina and Hyflo Supercel. Elution with benzene-chloroform (4 : 1) gave an inactive substance, m.p. 147-52°. The benzene-chloroform (1 : 1) fraction yielded an oil which crystallized from ether. Recrystallization from ether gave white crystals, m.p. 97-99°, ultraviolet absorption maxima at 260 mμ., and soluble in water.

Tested in Sabouraud agar medium, the antibiotic, designated S-39, showed activity against *Candida albicans* at $1:10^5$ dilution.

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SYNTHESIS OF PROCAINE HYDROCHLORIDE

Based on studies of cocaine degradation and the pharmacological activity of alkylaminobenzoates Einhorn[1] synthesized a series of effective local anaesthetic dialkylaminoalkyl esters. Of a series of alkyl-

p-aminobenzoate type compounds procaine showed the most favourable therapeutic ratio and is now a widely used local anaesthetic. Further, the procaine salt of penicillin was the first successful long-acting penicillin in extensive use even to-day, and hence the commerical importance of procaine.

Procaine has been synthesized by several methods which are subjects of a number of patents. With a view to prepare procaine hydrochloride on a commerical scale we have standardized a process for the preparation of β-diethylaminoethyl-*p*-nitrobenzoate hydrochloride and its direct reduction with Raney nickel. Several reducing agents such as Zn + HCl[1], Fe + HCl[2], Fe + AcOH[3,4] Sn+HCl[5,2], $SnCl_2$ + HCl[6] and electrolytic reduction[7] have been used in the earlier methods. Saito *et al*[8] employed activated nickel for the reduction of the nitro ester in acetone at 80-100° at 20 to 30 atmospheric pressure. In the present work the hydrochloride of the nitro ester in methanol or ethanol was reduced with Raney nickel at room temperature and 50 lbs. pressure, yielding procaine hydrochloride directly in an overall yield of 75 per cent starting from *p*-nitrotoluene. The advantages of the method are that the procaine hydrochloride is obtained directly in one stage by reduction of the corresponding nitro ester hydrochloride and secondly, the reduction of the ester is carried out at room temperature and relatively lower pressure.

EXPERIMENTAL

p-Nitrobenzoic acid[9]

p-Nitrotoluene (250 g.) was oxidized with potassium dichromate (750 g.) and concentrated sulphuric acid (900 ml.) in water (1.5 l) at 130° for 6 hr. After cooling, ice cold water (3 l.) was added and the precipitate filtered off, dissolved in 10% sodium hydroxide (1. 5 l.) and the solution filtered. The filtrate was acidified with 20% sulphuric acid (1 l.), and the precipitate of pure *p*-nitrobenzoic acid filtered, washed with water and dried ; m.p. 236°, yield 250 g. (90%).

p-Nitrobenzoyl Chloride

p-Nitrobenzoic acid (250 g.) was refluxed with thionyl chloride (150 ml.) on a water bath for 16 hr. Thionyl chloride was distilled off and *p*-nitrobenzoyl chloride crystallized from benzene ; m.p. 72°, yield 267 g. (98%).

Diethylaminoethyl-p-nitrobenzoate Hydrochloride

To *p*-nitrobenzoyl chloride (240 g.) in toluece (1.2 l.) diethylamonethanol (146 ml.) was gradually added and the mixture heated on a water bath for 1 hr. The precipitated hydrochloride of the nitro ester was filtered and washed with toluene (300 ml.) ; m.p. 127-28°, yield 380 g. (97%).

Procaine Hydrochloride

Diethylaminoethyl-*p*-nitrobenzoate hydrochloride (25 g.) in methanol (150 ml.) was reduced with Raney nickel (0.5 g.) at 50 lbs. pressure and room temperature (28-29°) for 16 hr. Excess of methanol and water was distilled off azeotropically with toluene after removing Raney nickel. The crude procaine hydrochloride was recrystallized from ethanol ; m.p. 152°, yield 19 g. (85%).

ACKNOWLEDGEMENT

The authors are thankful to Dr. R. Kaushal for his guidance and Dr. M. J. Thirumalachar for his interest in the work.

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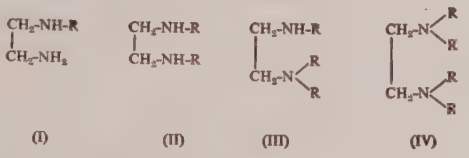
N, N'-DIBENZYLETHYLENEDIAMINE *

N, N'-dibenzylethylenediamine (II) is a base for the preparation of N, N'-dibenzylethylenediamine dipenicillin G (Benzathine penicillin), a stable repository penicillin salt ; it is also useful for the recovery, purification and preparing formulations of antibiotics.

Bleier[1] prepared (II) from dibenzenesulphonylethylenediamine ; Frost *et al*[2]., and Menziani *et al*[3]., prepared it, along with other by-products, by the condensation of benzylamine with ethylenedihalide; Hauslick *et al*[4]., alkylated dibenzalidene ethylenediamine with benzylchloride to produce (II). A widely used general method is the reduction of a Schiff's base derived from ethylenediamine and benzaldehyde with sodium and alcohol[5], or sodium amalgam[6] and catalytic hydrogenation using platinum oxide[7], supported palladium[8], or Raney nickel[9] at high temperatures and pressures, resulting very often in 1:3 dibenzyl-2- phenyltetrahydro imidazole which is further cleaved to give (II).



(I) (II) (III) (IV)

R = $-CH_2-C_6H_5$

In the present work, with a view to evolve a simple and economic process for the manufacture of (II), the condensation of ethylenediamine with benzylchloride without the use of alkali[10], has been studied under different conditions. The effects of varying molecular concentrations of the reactants, the period of addition, temperature, and the presence of solvents, on the course of the reaction were investigated to establish optimum conditions for satisfactory yields of (II). The reaction also produced N-monobenzylethylenediamine (I) in good yields (Cf. Aspinall *et al*[11]) which could be converted to (II). The principal advantage of the process is that (II) can be easily separated from the two layers after reaction is complete and directly distilled under reduced pressure without further treatment with water, alkali and extraction with an organic solvent. Further, ethylenediamine, which acts as a reactant as well as an acid binding agent, can be easily recovered for further use. The reaction products mono- (I), di- (II), tri- (III)

* Hindustan Antibiotics (P) Ltd. An improved process for the manufacture of N, N'-dibenzylethylenediamine. Indian Patent 62,439 (Sept. 2, 1958)

and tetrabenzylethylenediamine (IV) were characterized by their hydrochlorides and picrates.

Effect of Molecular Concentration of Reactants

When ethylenediamine was condensed with benzyl chloride in the molecular ratio 1 : 2, the main product was (IV) (Expt. 1, 2). The molecular concentration of benzylchloride was, therefore, kept constant and that of ethylenediamine gradually increased until the yield of (II) was maximum and that of the higher boiling fractions consisting of (III) and (IV) was minimum. Further increase in the concentration of ethylenediamine led to the formation of (I) in excess of (II) (Expt. 10).

With the molecular concentration ratio of ethylenediamine to benzylchloride at 1:2 or 3:4 the product was mainly (IV) (Expt. 4) ; at 1:1 ratio a small quantity of (II) and predominantly (IV) were formed (Expt. 5, 6). With 3:2 ratio the results were satisfactory but a fair amount of the higher boiling fractions were also produced (Expt. 7) ; a ratio of 2:1 was most favourable with a minimum of the higher boiling point fractions. With a 5:1 ratio the main product was (I) with a small amount of (II).

Effect of Solvent

Ethanol and benzene were used as solvents for the reaction. Both the solvents were of no particular advantage when the ratio of the reactants, ethylenediamine to benzylchloride, was 1:2 or 3:4 (Expt. 2, 4). Ethanol improved the yield of (II) when ratio of reactants was 1:1 (Expt. 5, 6). However, when the ratio was 2:1, ethanol lowered the yield of (II) (Expt. 9).

Period of Addition of Benzylchloride

In small scale experiments the period of addition of benzylchloride was short and of no consequence. But on a large scale, the addition was so regulated to avoid undue rise in temperature leading to formation of higher boiling fractions other than (II) and too slow addition resulting in (I).

Anhydrous ethylenediamine gave better yields of (II) (Expt. 15, 16) but on a larger scale it may be economical to use commercial monohydrate ethylenediamine, there being no appreciable difference in the yield taking into account factors such as the preparation of anhydrous ethylenediamine (Table II).

EXPERIMENTAL

General Procedure

1. Benzylchloride was gradually added to ethylenediamine with shaking and cooling. The mixture was heated on a steam bath for the prescribed period, cooled and treated with sodium hydroxide (10%). (If the solid separated it was filtered and crystallized from alcohol). The filtrate was extracted with ether, the ethereal solution dried over sodium hydroxide, the solvent evaporated and the residue distilled under reduced pressure at 2-3 mm. The different fractions were identified by preparation of the hydrochlorides by passing dry hydrochloric acid in ethereal solution and crystallization from alcohol or acetone.

	B. P./2-3 m.m.	M.P. Hydrochloride	M.P. Picrate
Monobenzylethylenediamine (I)	110-15°	253°[1]	221°[1]
N, N'-dibenzylethylenediamine (II)	186-200°	298°[1]	209-11°[1]
Tribenzylethylenediamine (III)	210-30° (m.p. 99°)	Indefinite	Indefinite[2]
Tetrabenzylethylenediamine (IV)	235-42 (m.p. 94.5°)	198-202°[12]	199-200°[12]

2. Benzylchloride was gradually added to ethylenediamine in alcohol or benzene with shaking and cooling. The reaction mixture was refluxed on steam bath for the prescribed period. If the solid separated it was filtered, treated with dilute alkali (10%) and crystallized from alcohol. The product, m.p. 94-95°, was identified as (IV) as it did not give Hinsberg and Liebermann reactions. The mother liquor was evaporated to remove solvent and further worked up as in 1.

3. Ethylenediamine and benzylchloride were distilled before use. To ethylenediamine monohydrate (78 g., 1. mol.) in a flask kept cool under running tap water, benzylchloride (63.3 g., 0.5 mol.) was gradually added within 20 min. so that the mixture warmed up only slightly. The mixture was heated on steam bath for 12 hr. with continuous stirring, and then transferred to a separatory funnel. The two layers were separated, treated with sodium hydroxide pellets and the liquid fractionated. The lower layer on fractionation gave ethylenediamine, b.p. 118-20°, yield 58 g. ; the upper layer on fractionation at 2-3 m.m. pressure gave (I), b.p. 110-15°, yield 15 g. ; (II), b.p. 186-200°, yield 25 g. (42% calculated on the amount of benzylchloride used); (III), b.p. 210-30°, yield 3 g. About 3 g. of (II) could be recovered by treating the alkaline solid residue with water, extraction with ether and working up as in 1.

4. N-benzylethylenediamine (15 g.) was mixed with benzylchloride (6.3 g.) and heated on steam bath for 12 hr. The mixture was then treated with sodium hydroxide solution (10%), extracted with ether and dried over sodium hydroxide. The residue, on evaporation of ether, gave (II), b.p. 186-200° /2-3 mm., yield 6 g.

ACKNOWLEDGEMENT

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TABLE I

Condensation of Ethylenediamine with Benzylchloride

Expt. No.	Reactants		Solvents		Period of heating on steam bath	Benzylethylenediamine			
	Ethylenediamine monohydrate	Benzyl-chloride	Alcohol	Benzene		Mono-	Di-	Tri-	Tetra-
1.	3.9 g. (0.05 mol)	12.65. g. (0.1 mol.)	—	—	6 hr.	—	—	—	7.0 g.
2.	„ „	„	—	50 ml.	„	—	—	—	7.8 g.
3.	5.85 g. (0.075 mol)	„	—	—	5 hr.	—	—	—	11.2 g.
4.	„ „	„	40 ml.	—	3 hr.	—	—	—	10.2 g.
5.	7.8 g. (0.1 mol.)	„	—	—	7 hr.	—	0.7 g.	—	8.0 g.
6.	„ „	„	50 ml.	—	5 hr.	—	3.0 g.	—	2.1 g.
7.	11.7 g. (0.15 mol.)	„	—	—	12 hr.	—	4.1 g.	2.12 g.	—
8.	15.6 g. (0.2 mol)	„	—	—	6 hr.	2.0 g.	4.5 g.	0. 5 g.	—
9.	„ „	„	60 ml.	—	3.5 hr.	—	3.5 g.	—	—
10.	„ „	5.06 g. (0.04 mol)	—	—	7.5 hr.	4.0 g.	2.0 g.	—	—

LARGE SCALE EXPERIMENTS

Condensation of Ethylenediamine with Benzylchloride

Expt. No.	Ethylene-diamine	Benzyl-chloride	Benzyl-chloride addition period	External cooling with tap water	Recovery of Ethylene-diamine	N, N'-Benzylethylenediamine Mono- (I)	Di- (II)	Tri- (III)	Tetra- (IV)	Remarks
	Monohydrate									
11	78.0 g. (1 mol.)	63.25 g. (0.5 mol.)	20 min.	Yes	58.0 g.	15.0 g.	25.0 g.	3.0 g.		No appreciable diff. without cooling and slow addition.
12	„	„	„	No	62.0 g.	12.0 g.	24.0 g.	4.0 g.		
13	156.0 g. (2 mol.)	126.5 g. (1 mol.)	10 min.	No	134.0 g.	18.5 g.	51.7 g.	12.0 g.	21.0 g.	No cooling, period of addition short; higher yield of (III), (IV)
14	390.0 g. (5 mol.)	316.25 g. (2.5 mol.)	25 min.	Yes	266.0 g.	137.0 g.	138.0 g.	12.0 g.	31.0 g.	Cooling, slow addition; good yields of (I), (II)
	Anhydrous									
15	36.0 g. (0.6 mol.	63.25 g. (0.5 mol.)	10 min.	Yes	4.0 g.	8.2 g.	24.0 g.	17.3 g.	4.0 g.	Cooling, period of addition short, amt. of ethylene-diamine small; high yields of (III), (IV)
16	60.0 g. (1 mol.)	„	10 min.	Yes	32.0 g.	14.0 g.	29.0 g.	—	—	Cf. expt. 11; slightly better yield of (II)
17		„	35 min.	Yes.	28.0 g.	22.0 g.	22.0 g.	6.0 g.	3.0 g.	Same as above, but period of addition long, yield of (I) high
18	„	„	2 min.	Yes	32.0 g.	15.0 g.	29.0 g.	4.0 g.	5.0 g.	Cf. expt. 17; period of addition very short.

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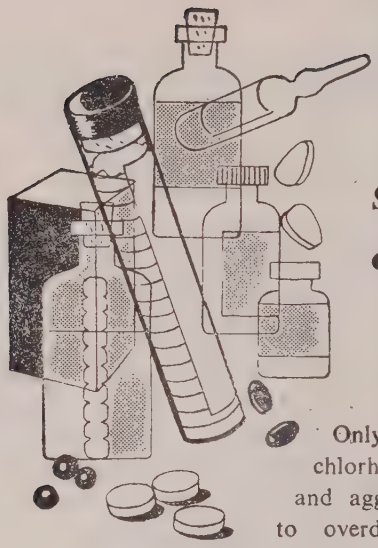

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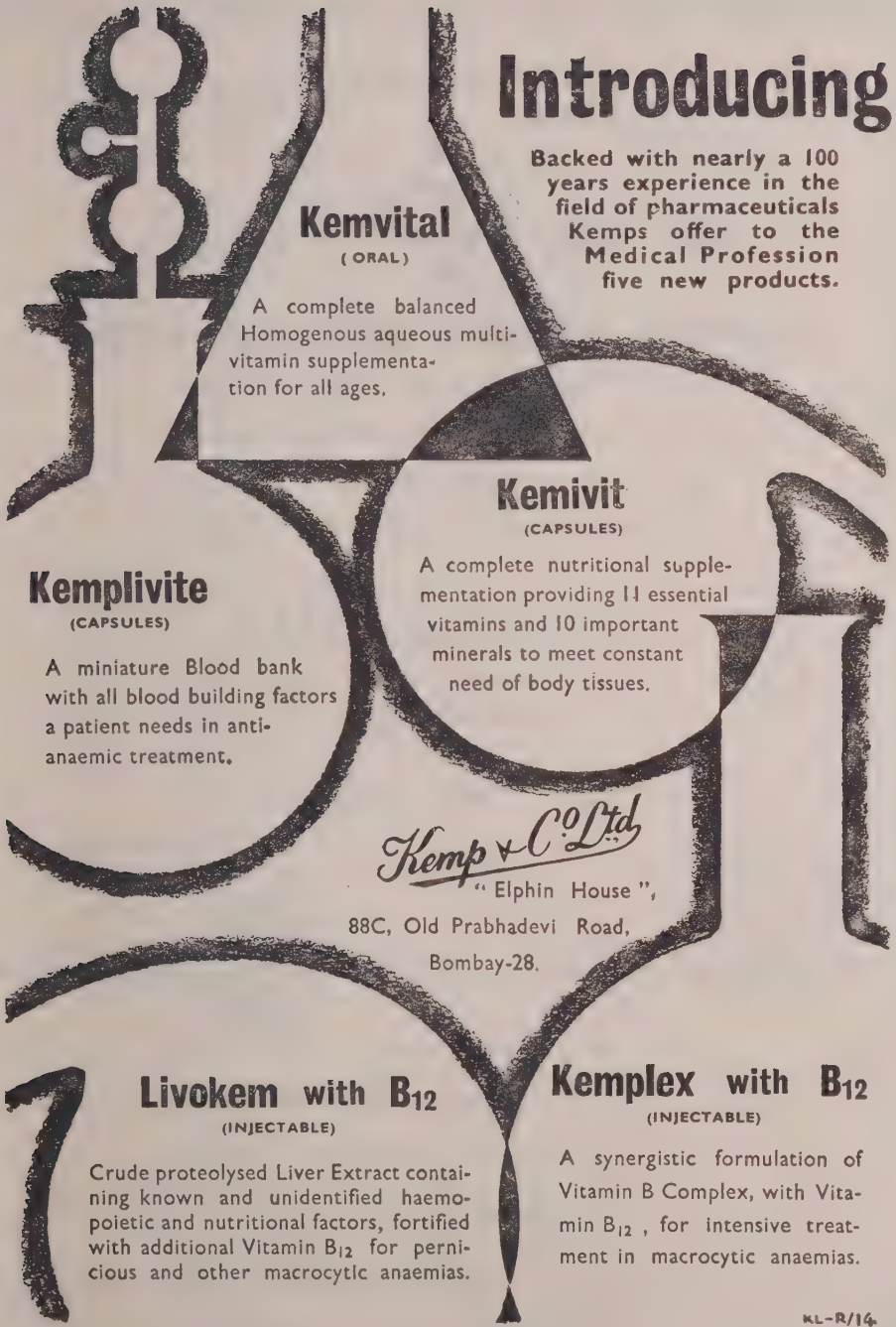
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Physico-chemical Data on Antibiotics

I. ANTIBIOTICS PRODUCED BY FUNGI, BACTERIA AND LICHENS

1. Melting Points and Ultraviolet Absorption Maxima

Antibiotic activity has been reported for a large number (over 5,000) of microbial culture filtrates and crude substances, but certain amount of chemical, physical and biological data are available only for about 735 antibiotics. As an aid in the identification and study of antibiotics, tables classifying such compounds by physical, chemical and biological data have been compiled. Summaries of the tabulated data will be published in a series of papers. The present compilation is concerned with the physical and chemical properties (melting point, ultraviolet absorption maxima, and empirical formula) of antibiotics produced by bacteria, fungi and moulds, and lichen. Of the 430 antibiotics produced by these groups of organisms, the above data have been reported for about 235 compounds.

Source Organisms	Number of Antibiotics
Bacteria	110
Actinomycetes	305
Fungi and moulds	290
Lichen	30
	735

In the appended list, the antibiotics are arranged by their empirical formulae, the order being C, H, N, O, Cl, S, other components. The empirical formula being known only for compounds 1-182 the arrangement from serial number 183 onwards is alphabetically by the producing organism. For each antibiotic listed the following data are given : Empirical formula, producing organism, crystal form and colour, nature, melting point, ultraviolet absorption maxima, optical rotation, antibiotic activity and whether the structural formula is known or not.

In Chart 1 for melting points, the serial numbers (S. No.) from the list just mentioned are posted in the squares headed by the relevant melting point range so that S. Nos. of antibiotics having the same melting point range fall in the same square. For example, antibiotics melting in the range 110-115° are those with S. Nos. 6 and185, *i.e.* Patulin and Gigantin.

In Chart 2 for ultraviolet maxima, each square represents one wavelength in mμ on the horizontal side in units (0 to 9) and the numbers (210, 220 etc.) in first vertical column denote the beginning of the range. S. Nos. of antibiotics are posted in the appropriate squares such that those compounds having the same u.v. maxima fall in the same square. For instance, antibiotics with u.v. maxima 235 mμ are those at S. Nos. 52 and 78 *i.e.* Hydroaspergillic acid and Illudin S.

The charts and tests are also helpful in the study of antibiotics as groups of compounds having certain defined chemical-physical properties.

Literature references have been omitted to save space. They are, however, available in comprehensive compilations as:

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ABBREVIATIONS AND SYMBOLS

An aesterick Following a S. No. indicates that the structural formula of the compound is known.

A. = *Aspergillus* P. = *Penicillium*

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A. NEELAMEGHAN.

CHART 1. MELTING POINT (°C) RANGES

M.P.	25 — 30	30 — 35	35 — 40	40 — 45	45 — 50	50 — 55	55— 60	60 — 65	65 — 70	70 — 75
S.Nos.		26	91		36	70	29	21 32	33	130 218
M.P.	75 — 80	80 — 85	85 — 90	90 — 95	95 —100	100 — 105	105 — 110	110 — 115	115 — 120	120 — 125
S.Nos.	144 210	131	21 167 44 149	11* 38 57	51	8	34 153 124 125 136	6 185	5 17 121 214	7 123 64 146 78 148 85 209
M.P.	125 —130	130 —135	135 —140	140 —145	145 —150	150 —155	155 —160	160 —165	165 —170	170 —175
S.Nos.	7 160 85 120 159	11 89 54 101 65 108 77 137	22 150 111 154 134 155 135	89 169 99 231 117	10* 114 52 140 88 166 100 207	87* 4 110 157 129	47 221 73 186 220	18* 67 23 145 42 53	95 219	3 58 142 15 75 143 30 139 37 141
M.P.	175 —180	180 —185	185 —190	190 —195	195 —200	200 —205	205 —210	210 —215	215 —220	220 —225
S.Nos.	79 98 173	31 113 147 224	115 122 128	96 107 152 158	9* 119 12* 195 56	19 102 60 107 63* 126 94	71 127 76 133 92 156 109	72 132 108 165 115 116	83 206 84* 97 106	43 118 82 165 116 189 117
M.P.	225 —230	230 —235	235 —240	240 —245	245 —250	250 —255	255 —260	260 —265	265 —270	270 —275
S.Nos.	28 93 188 35 151 191 55 170*208 59 182 92	27 93 184 74 170*228 80 172 86*174	48 181	104 176 225	175	20* 163 222*	138 175 192	103*	69 105 175 229	187
M.P.	275 —280	280 —285	285 —290	290 —295	295 —300	300 —305	305 —310	310 —315	315 —320	320 —325
S.Nos.		193	164	62 162	24	13 171*			14 81	68
M.P.	325 — 330	330 —335	335 —340	340 —345	345 —350	350 —355	355 —360	360 —365	365 —370	Above 375
S.Nos.						168	61	196 217		1

*(9) Explodes
(10) Darkens, sublimes
(11) Dec., explodes
(12) Explodes
(18) Chars above 160
(20) Appears to melt at 252
(63) (84) (86) (87) Na salt
(102) Chars on heating
(103) Carbonises
(170) Sulphate 226-28; HCl 332-36 dec.
(171) Above 300
(222) Above 250 dec.

CHART 2. ULTRAVIOLET ABSORPTION MAXIMA

λMax	0	1	2	3	4	5	6	7	8	9
210	39 41	166 207 208 253	29	7			7 129	70 214		
220	121	26			53	12 69	69 129		70 107[2]	
230	9 77 121 165	165	88 89 111		51 165	52 78	39 53 88 111	41 70	161 215	158 161
240	9 230	18 70 75 116	72 88 100 117	104	111	75	29 53 57 75	26	39 75	41
250	30 127 40 194 58 198 69 201 98	104 215	84 173	178 180 199 200 211		37 183		129	84 85 89 110 173 183[3]	60 214 226
260	3 110 12 204 35 230 75 88a	27	13 39 53	31 41 161 227	27 84 173	213 215	110 115	42 110 113 161	73 85 198 201	
270	9 203 14 205 56 85	182	216	135 190 212	85 214 226 227	12 130 24 223[4] 32 232 42 91	6 39 85 213	41 197	40 86 202	57
280	69 211 215	129	182		92 93 107	9	70 97 98	83	200	36 129
290	69 227 142 176 177 214	12 182 226		26	213		129 197	211	30[1]	

(1) 297-300 mμ (2) 226-230 mμ (3) 255-260 mμ (4) 270-280 mμ

λMax	0	1	2	3	4	5	6	7	8	9
300	88 111	5 26		9	117 158	18 116 42 69 71 72		110		214
310	3 12 37 226 227	70		213	4 29 53 88 111	70	75[1] 88 111 211	24		
320	69 77 104 110		158 165	9 70 113 115		97 98 121 131	110	57	51 111 52 53 78 88	
330	58 69 100	70	13		121		129 158	129	110	211
340	64 69 89			42		20 151				
350	14	158								
360	13 53					196				
370		129							196 223[2]	
380						40				
390	70	70							70	
400	196					3		32 70 130		

(1) 314-318 mμ

(2) 375-380 mμ

λmax	0	1	2	3	4	5	6	7	8	9
410										
420	60									
430	70									
440										
450						70 223[1]				
460										129
470		129								
480										
490										
500						71 72				
510										
520								70		
530						129[2]				129
540		70 129								
550										

(1) 450-460 mμ

(2) 535-540 mμ

S. No.	Empirical formula. Antibiotic.	Produced by	Chemical nature. Melting point (°C)	U. V. absorption maxima (λ max) m μ Optical rotation $(\alpha)_D$	Active mainly against (organisms)
1	2	3	4	5	6
1	$C_5H_4O_2$ Albidin	**P. albidum**	Glistening red needles. Red pigment. Darkens at 120, no melting at 380.		Fungi. Weak against bacteria
2	$C_5H_6O_3$ Mycoine C_1	**Penicillium** spp. **Acetobacter** spp. **Aspergillus** spp.			Gram+, gram—, acid fast
3*	$C_6H_6N_2O_4$ Toxoflavin	**Bacillus cocovenans**	Yellow cryst. 172	260, 310, 405 (pH 6. 5)	Gram+, gram—
4*	$C_6H_6O_4$ Kojic acid	**Acetobacter** sp. **Aspergillus** sp. **P. daleae**	Colourless prisms. 151-54.	314 (aq. neut. or alk. soln.) Opt. inactive.	Weak against gram+and gram—
5*	$C_7H_6O_2Cl$. Drosophilin A	**Drosophila subatrata**	White cryst. Acidic. p-Methoxytetrachlorophenol. 118 cor.	301. Opt. inactive.	Gram+, **M. smegmatis, YSK** polio virus, phage Weak against gram—
6*	$C_7H_6O_4$ Patulin	**Aspergillus** and **Penicillium** spp.	Colourless rhomboid plates or prisms. Neutral. 109-12.	276. Opt. inactive.	Gram+, gram—, carcinoma cells in tissue culture
7	$C_7H_6O_4$ Terreic acid	**A. terreus**	Colourless or pale yellow large shining plates. 120-21; 127-127. 5.	213, 216. —16 (c, 1 $CHCl_3$, 22°); —28 6(c,1 50% CH_3OH—50% C_6H_6); +74.3 phosphate buffer, pH 7).	Gram+, gram—, fungi, **T. vaginalis**
8*	$C_7H_8O_3$ Gentisyl alcohol	**Penicillium** spp.	Colourless needles. 100-101.		Weak against gram+
9*	$C_8H_3NO_2$ Diatretyne 2	**Ciltocybe diatreta**	Polyacetylene. 198 uncor., explodes.	230, 240, 270, 285, 303, 323 (95% EtOH).	Activity due to contamination with Diatretyne 1 (12)
10*	$C_8H_4O_3$ Nudic Acid B	**Tricholoma nudum**	Small colourless needles. 150 darkens, sublimes.	Opt. active in alcohol.	Gram+, gram—
11*	$C_8H_5NO_2$ Agrocybin	**Agrocybe dura**	White cryst. Neutral, weakly acidic. Acetylenic. 90 dec. explodes in vacuo; 130-40 dec. explodes in air.	Opt. inactive.	Gram+, gram—, fungi.

1	2	3	4	5	6
12*	$C_8H_5NO_3$ Diatretyne 1	**Clitocybe diatreta**	198 uncor., explodes	225, 260, 275, 291, 310 (95% EtOH)	Gram+
13*	$C_8H_6O_5$ Stipitatic acid	**Penicillium stipitatum**	Cream coloured cryst. Dibasic acid. 302-304 dec.	262, 332, 360 (water) Opt. inactive.	Fungi.
14*	$C_8H_6O_6$ Puberulic acid	**P. puberulum**, other **Penicillium** spp.	Colourless microcrystalline plates. Dibasic acid. 316-20 dec.	270, 350.	Gram+
15*	$C_8H_8O_3$ 6-Methylsalicylic acid	**P. claviforme**	170-71.		Fungi.
16*	$C_8H_8O_3$ 5-Methoxy-p-toluquinone	**Lentinus degener, Coprinus similis**	Golden yellow plates, clusters of short prisms. Quinone.		Gram+, gram—, acid fast
17*	$C_8H_8O_4$ Fumigatin	**A. fumigatus**	Maroon needles. Pigmented quinone. 116.		Gram+, gram—
18	$C_8H_8O_5$ Fomecin A	**Fomes juniperinus**	Cryst. depend on solvent. Weakly acidic. Chars above 160.	241, 305 (95% EtOH). Opt. inactive.	Gram+, influenza virus A. Slight activity against gram—, fungi.
19*	$C_8H_8O_5$ Spinulosin	**P. spinulosum** **A. fumigatus**	Purplish bronze or black plates. Quinone. 201-203·5.	Opt. inactive.	Gram+. Lower activity against gram—, acid fast
20	$C_8H_9N_2O_2S$ Micrococcin P	**Bacillus pumilus**	White cryst. solid. Discolours at 232, sinters at 238, appears to melt at 252.	345 (EtOH). +63·7 (c, 1·19 90% EtOH, 21°)	Gram+, **M. tuberculosis**
21*	$C_6H_{10}O_4$ Penicillic acid	**Penicillium** spp. **Arpergillus** spp.	Colourless rhomboid plates or prisms. Monobasic acid. 64-65 (hydrate); 86-87 (anhydrous).	Opt. inactive.	Gram+, gram—, fungi.
22	$C_8H_{10}O_4$ Antibiotic	**A. japonicus**	134-41 dec. (quinine salt).		**Zygosaccharomyces sulsus**
23	$C_8H_{13}NO_5$ Oryzasizine	**A. oryzae**	White hygroscopic needles. 162-63 dec.	—138; —133 (13. 5°)	Sake putrefying bacteria

1	2	3	4	5	6
24*	$C_9H_4O_7$ Puberulonic acid	**P. puberulum**, other **Penicillium** spp.	Yellow plates, prisms. needles. Dibasic acid. 296-98 dec.	274.5, 317	Gram+, less active against gram—.
25	$C_9C_8OS_2$ Mycoine C_2	**Acetobacter** spp. **Penicillium** spp. **Aspergillus** spp.			Gram+, gram—, acid fast
26*	$C_9H_8O_2$ 5-Methoxycoumarone	**Stereum subpileatum**	Colourless, shining leaflets. 34.	221, 247, 293, 300.5 (EtOH)	**Staph. aureus, E. coli**
27*	$C_9H_8O_5$ Flavipin	**A. flavipes** **A. terreus**	1: 2-diformyl-4:5:6- trihydroxy-3-methylbenzene. 233-34 dec.	261, 264 (dioxan).	Fungi
28*	$C_9H_{13}N_3O_7$ Lycomarasmin	**Fusarium lycopersici**	White microcryst. powder Acidic peptide. 227-29.	—42 to —48 (aq. soln., pH 7).	**Lactobacillus casei, Botrytis allii**
29*	$C_{10}H_{10}O_3$ Mellein	**A. melleus** **A. ochraceus**	Colourless needles. Lactone of 6-hydroxy-2-∝-hydroxypropyl-benzoic acid 56-57; 58.	212, 246, 314 (EtOH) —108.15 ($CHCl_3$, 12°)	**M. pyogenes var. aureus**
30*	$C_{10}H_{10}O_4$ Quadrilineatin	**A. quadrilineatus**	Colourless needles. Phthalaldehyde. 172 dec.	250, 297-300	**Botrytis allii, Pythium debaryanum**
31*	$C_{10}H_{12}N_4O_4$ Nebularine	**Ciltocybe nebularis**	Long prisms, small rhombohedral cryst. Neutral. Furanoside. 181-82-cor.	263 (water). —48.6 (c, 1 water, 25°);—61 (c, 0.8 0.1N NaOH, 25°), —22 (c, 0.8 0 1 N HCl. 25°) —47.5 (c, 2 water, 20°) —47.3 (c, 1 water, 20°)	Acid fast. Suppressive effect on ascites tumour in mice
32*	$C_{10}H_{12}O_4$ Aurantiogliocladin	**Gliocladium roseum**	Large orange leaflets. p-Benzoquinone. 63.	275, 407.	**B. subtilis, Botrytis allii**
33*	$C_{10}H_{12}O_4$ Sparassol	**Sparassis ramosa**	Colourless needles. 67-68		Weak activity on fungi
34*	$C_{10}H_{13}NO_2$ Fusaric acid	**Gibberella fujikuroi**	Colourless plates. Acid related to nicotinic acid 108-109.		Weakly bacteriostatic

1	2	3	4	5	6
35*	$C_{10}H_{13}N_5O_3$ Cordycepin	**Cordyceps militaris**	Colourless needles or plates. 225-26.	260 (EtOH). —47 (water, 20°)	**B. subtilis, Myco. avium**
36*	$C_{10}H_{14}O_4$ Gliorosein	**Gliocladium roseum**	Colourless needles. 48.	289.	Low activity against bacteria
37*	$C_{11}H_7NO_3Cl_2$ Pyoluteorin	**Pseudomonas aeruginosa**	174-75 dec.	255, 310. Opt. inactive.	Gram+, gram—
38*	$C_{11}H_8O_2$ 6-Methyl-1, 4-napthoquinone	**Marasmius graminum**	Golden yellow needles. 90-91.		**M. pyogenes** var. **aureus**
39*	$C_{11}H_8O_2$ Nemotin	**Poria corticola, P. tenuis**	Neutral. Acetylenic.	207, 236, 248,262,276 (water) +202 (c, 1.2 EtOH); +350 (alcohol, 17°).	Gram+, gram—, fungi
40*	$C_{11}H_8O_3$ Phthiocol	**M. tuberculosis**	Bright yellow prisms. Naphthoquinone pigment.	250, 278, 385 (95% alcohol)	Gram+, gram—
41*	$C_{11}H_{10}O_3$ Nemotinic acid	**Poria corticola, P. tenuis**	Monobasic acid. Acetylenic	208, 237, 249, 263, 277 (water). +270 (c, 0.44 EtOH, 23°); +380 (alcohol, 17°).	Same as Nemotin (39), but less active against fungi.
42*	$C_{11}H_{10}O_5$ Gladiolic acid	**P. gladioli**	Colourless, long, silky needles. Monobasic carboxylic acid. 160.	275, 343 (0·1N NaOH). 267, 305 (Lactol form). Opt. inactive.	Fungi.
43*	$C_{11}H_{10}O_6$ Cyclopaldic acid	**P. cyclopium**	Colourless, long, fluffy needles. Dibasic acid 224-25.		**Botrytis allii**
44	$C_{11}H_{15}NO_3$ Candidulin	**A. candidus**	Long, white needles. Neutral. Non-aromatic. 88-89 uncor.	No characteristic spectrum. +15±2 (c, 1 $CHCl_3$, 24°).	Gram+, gram—, fungi.
45	$C_{11}H_{15}O_3$ Tardin	**P. tardum**	Pale yellow oil.	—11·4 (alcohol, 20°)	Gram+, fungi
46	$C_{11}H_{22}O_3$ Pyolipic acid	**Pseudomonas aeruginosa**	Colourless, odourless, viscous oil. Acidic lipoid containing DL-β-hydroxydecanoic acid and a carbohydrate.	—18·9 (20°)	**Myco. tuberculosis**

1	2	3	4	5	6
47*	$C_{12}H_8N_2O$ Hemipyocyanine	**Pseudomonas aeruginosa**	Yellow, needles. Pigment, ∝-hydroxyphenazine. 158.		Gram+, gram—, fungi
48*	$C_{12}H_8N_2O_4$ Iodinin	**Chromobacterium iodinum**	Purple cryst. with coppery glint. Pigment. 236 dec.		Gram+
	$C_{12}H_{17}NO_3$ Candidulin (See 44)				
49	$C_{12}H_{18\text{-}20}N_2O_{3\text{-}5}$ Fluvomycin	**Bacillus subtilis**	White amorphous powder. Weakly acidic; probably polypeptide.		Gram+, gram—, fungi
50	$C_{12}H_{20}N_2O_2$ Granegillin	**Aspergillus** sp.	Resembles Aspergillic acid (51).		Gram—, low activity against gram+
51*	$C_{12}H_{20}N_2O_3$ Aspergillic acid	**A. flavus**	Yellow needles in radial clusters. Monobasic acid. 97-99.	234, 328 +13.4 (c, 0·85EtOH, 24°); +18.5 (c, 1·05 1N NaOH, 24°)	Gram+, gram—, acid fast
52*	$C_{12}H_{20}H_2O_3$ Hydroaspergillic acid	**A. flavus**	Almost colourless needles. Monobasic acid. 149-50	235, 328. +36 (c, 1.0 EtOH)	Weakly antibacterial
53	$C_{12}H_{20}N_2O_3$ Neohydroxyaspergillic acid	**A. sclerotiorum**	Colourless, irregular platelets. Cyclic hydroxamic acid. 164-66.	236, 328 (EtOH) 246, 360 (0.1N HCl). 224, 262, 314 (hexane)	Gram+, gram—, acid fast, fungi, phage
54*	$C_{13}H_{10}N_2O$ Pyocyanine	**Pseudomonas aeruginosa**	Dark blue needles. Basic blue pigment. 130 dec.		Gram+, gram—, fungi
55*	$C_{13}H_{10}N_3O$ Chlororaphin	**Pseudomonas chlororaphis**	Green cryst. Green pigment. 225-30 dec.		Hemolytic streptococci
56*	$C_{13}H_{14}N_2O_4S_2$ Gliotoxin	**A. fumigatus**, other fungi	Colourless, long plates or needles. 195.	270. —239 — to —256 ($CHCl_3$);—290±10 (0.078 EtOH, 25°)	Gram+, gram—, fungi, sarcoma implants

1	2	3	4	5	6
57	$C_{13}H_{14}O_3$ Diaporthin	**Endothia parasitica**	Colourless cryst. 91.5-92.5 cor.	246, 279, 327 +58 (c, 1 $CHCl_3$)	**B. subtilis**, fungi
58*	$C_{13}H_{14}O_5$ Citrinin	**P. citrinum**, other **Penicillium** and **Aspergillus** spp.	Golden prismatic needles or serrate plates. Monobasic acid. 170, 175 dec.	250, 330 $(\alpha)_{5461}^{23}$—43.1 (c, 0.92 absol. EtOH);—37.4 (c, 1.15 EtOH, 18°)	Gram+
59*	$C_{14}H_{10}O_4$ Phenicin	**P. phoenicum, P. rubrum**	Yellow-brown, long rectangular tablets. Dibasic acid pigment. 229-31.		Gram+, **Myco. phlei**
60*	$C_{14}H_{10}O_4Cl_2$ Mollisin	**Mollisia caesia, M. fallens**	Orange yellow needles. 202-203.	259, 280sh, 420, (5.4 mg. in 0.5 mol. $CHCl_3$) Opt. inactive.	Fungi
61*	$C_{14}H_{10}O_5$ Alternariol	**Alternaria tenuis**	Colourless needles Substituted dibenzo-α-pyrone. 350 dec.		**M. pyogenes** var. **aureus E. coli**
62*	$C_{14}H_{10}O_7.2H_2O$ Citromycetin	**P. frequentans**	Yellow cryst. Dibasic acid. 290–300 dec.	Opt. inactive.	**M. pyogenes** var. **aureus**
63*	$C_{14}H_{20}N_2O_4S$ Pentenyl penicillin (Penicillin F)	**P. notatum, Penicillium** spp., **Aspergillus** spp.	Colourless prisms. Monobasic carboxylic acid. 204-205 dec. (Na salt)	No characteristic bands. +276 to +316 (c, 0.821 water, 20-25°).	Gram+, spp. of **Treponema, Borrelia, Leptospira**
64	$C_{14}H_{20}O_3$ Nudic acid A	**Tricholoma nudum**	Colourless needles or plates. 123.5 uncor.	Active in alcohol.	Gram+, gram—
65	$C_{14}H_{20}O_4$ Frequentin	**P. frequentans**	Colourless needles. Aldehyde. 134.5 dec.	+82 ($CHCl_3$, 24°)	Fungi, low activity against bacteria
66*	$C_{14}H_{21}N_3O_6S$ Synnematin B; Cephalosporin N	**Cephalosporium salmosynnematum**	Ba salt: White powder. Hydrophilic penicillin, containing D-α-aminoadipic acid.	Ba salt :+187(c, 0·6 water, 20°).	Gram+, gram—. **Myco. tuberculosis** at higher conc.
67*	$C_{14}H_{22}O_4$ Palitantin	**P. palitans**	Colourless needles. Unsaturated dihydroxy aldehyde (Cf. frequentin). 163.	$(\alpha)_{5461}^{23}$:+4.4 (c, 0.8, $CHCl_3$).	

1	2	3	4	5	6
68*	$C_{15}H_{10}O_5$ Strepsilin	**Cladonia streptilis**	Long prisms or needles. Dibenzofuran derivative. 324.		**Staph. aureus, Myco. tuberculosis**
69	$C_{15}H_{11}NO_2$ Viridicatin	**P. viridicatum. P. cyclopium**	Colourless cryst.; lustrous needles (from EtOH); prisms (from other solvents) 269	225, 280, 305, 320, 330 (EtOH) 226, 250, 290, 330, 340 (aq. NaOH). No rotation	**Myco. tuberculosis**
70*	$C_{15}H_{14}O$ Lactaroviolin	**Lactarius deliciosus**	Violet red pigment. Azulenealdehyde. 53	24[illegible], 311, 390, 541 (cyclohexane). 242, 315, 398, 527 (alcohol). 286, 331, 407, 455 (formic acid). 217, 228, 237, 323, 391, 430 (50% H_2SO_4)	**Myco. tuberculosis**
71*	$C_{15}H_{14}O_6$ Javanicin	**Fusarium javanicum**	Red laths with coppery lustre Weak monobasic acid. 207.5-208 dec.	305, 505 (EtOH) Opt. inactive.	Gram+, acid fast
72*	$C_{15}H_{14}O_7$ Oxyjavanicin	**Fusarium javanicum**	Red needles with coppery lustre 212; 213-16 dec.	305, 505 (EtOH) Opt. inactive.	Gram+, acid fast
73*	$C_{15}H_{16}N_2O_5S_2$ Gliotoxin monoacetate	**P. terlikowski**	Pale yellow rhombic cryst. 159-60	268 —197 (c, 0.6 $CHCl_3$, 19°)	Same as for Gliotoxin (56) but only one-tenth activity
74*	$C_{15}H_{16}O_5$ Fuscin	**Oidiodendron fuscum**	Orange, diamond-shaped plates. Quinonoid pigment. 230	Opt. inactive.	Gram+, low activity against gram—
75	$C_{15}H_{18}O_4$ Marasmic acid	**Marasmius conigenus**	White, long needles. Monobasic acid. 174-75 cor. (in sealed capillary in vacuo).	240-242, 314-318 (EtOH). 245, 246, 248, 260 (phosphate buffer, pH 1.45-3.52, 5.4, 8.8, 11.0). +176 (c, 1.4 C_3H_6O, 25°)	Gram+, acid fast, less active against gram—. Fungi.
76*	$C_{15}H_{18}O_5$ Dihydrofuscin	**Oidiodendron fuscum**	Colourless rhombic cryst. Quinol. 206 dec.	Opt. inactive.	Gram+, gram—
77	$C_{15}H_{20}O_3$ Illudin M	**Ciltocybe illudens**	Neutral 130-31 uncor.	230, 320, (EtOH). —126 (absol. EtOH, 20°).	Acid fast. Weak antifungal activity

1	2	3	4	5	6
78	$C_{15}H_{20}O_4$ Illudin S	**Ciltocybe illudens**	Neutral 124-25	235, 328 (EtOH) —165 (absol. EtOH, 20°).	Gram+, acid fast
79	$C_{15}H_{20}O_4$ Hirsutic acid C	**Stereum hirsutum**	Colourless, large prisms 179.5 uncor.	None. +11.9 (free acid in absol. alcohol, 20°)	Inactive precursor of active acids.
80*	$C_{16}H_{10}O_5Cl_4$ Diploicin	**Buellia canescens**	Colourless coral form cryst. Depsidone of orcinol group. 232		**C. diphtheriae mitis**, acid fast.
81*	$C_{16}H_{10}O_7$ Endocrocin	**A. amstelodami** **Nephromopsis endocrocea**	Orange red cryst. Quinone 318		**Staph. aureus**
82	$C_{16}H_{14}O_6Cl_2$ Estin	**P. paxilli** var. **echinulatum**	223-25		**M. pyogenes** var. **aureus**, **Myco. tuberculosis**
83	$C_6H_7N_3O_4S_2$ Chaetomin	**Chaetomium** spp.	White non-cryst. powder. Neutral? 215; 218-20 dec.	287. +360 (c, 1 $CHCl_3$, 22°).	Gram+, acid fast
84*	$C_{16}H_{18}N_2O_4S$ Benzylpenicillin (Penicillin G)	**P. notatum**, other **Penicillium, Aspergillus** spp.	Colourless prisms Monobasic carboxylic acid 215 dec. (Na salt)	252, 257.5, 264 +305 (c, 0.821 water, 25°); +301 (c, 2 water, 25°)	Gram+, spp. of **Treponema**. **Borrelia**, **Leptospira**
85*	$C_{16}H_{18}N_2O_5S$ Phenoxymethyl penicillin (Penicillin V)	As for penicillin G (84)	Colourless prisms Monobasic carboxylic acid 120-28	268, 274 (water) 270, 276 ($CHCl_3$)	As for penicillin G (84)
86*	$C_6H_{18}N_2O_5S$ p-Hydroxybenzyl penicillin (Penicillin X)	As for penicillin G (84)	Colourless prisms Monobasic carboxylic acid 228-35 dec. (Na salt)	278. +267 (c, 0.525 water).	As for penicillin G (84)
87*	$C_{16}H_8N_2O_6S$ p-Hydroxyphenoxymethyl penicillin	**P. chrysogenum**	Colourless prisms 151-59 dec. (Na salt)	+215 (c, 1.06 Na salt in water)	As for penicillin G. (84)
88	$C_{16}H_{21}NO$ Pyo Ib	**Pseudomonas aeruginosa**	Colourless cryst. 2-Heptyl-4-quinolinol 146.2-147	236, 316, 328 (95% EtOH); 232, 300 (ethanolic HCl); 242, 314 (ethanolic KOH)	
88a	$C_{16}H_{21}N_3O_8S$ Cephalosporin C	**Cephalosporium** sp.	Na salts: Monoclinic cryst. Hydrophilic penicillin containing D-α-amino-adipic acid	260 +103 (c, 0.9 water, 20°)	**Staph. aureus, Salm. typhi** (1/10 activity of Cephalosporin N (66))

1	2	3	4	5	6
89	$C_6H_{23}NO_3$ Pyo IV	**Pseudomonas aeruginosa**	Colourless needles 131-32;139.5-140	232, 258, 340 (95% EtOH)	
90*	$C_{16}H_{26}N_2O_4S$ n-Heptyl penicillin (Penicillin K)	As for penicillin G (84)	Colourless prisms Monobasic carboxylic acid	No characteristic spectrum. +258 (c, 0.43 water, 25°)	As for penicillin G (84)
91	$C_{16}H_{28}O_2$ Grifolin	**Grifola confluens**	Colourless fine needles 40	275. Complete transmission above 300	Gram+, less active against gram— and acid fast
92	$C_{17}H_{12}O_7Cl_3$ Geodin-like antibiotic	**A. flavipes**	Pale yellow elongated microprisms Dibasic acid 208 (form I), 229-30 (form II)	284. +175 ($CHCl_3$, 20°)	Gram+, **Myco. pseudotuberculosis**
93*	$C_{17}H_{12}O_7Cl_3$ Geodin	**A. terreus**	Brown or yellow needles 227-30; 235 dec.	284. $(\alpha)^{20}_{5461}$ +179(c,0.8$CHCl_3$); $(\alpha)^{20}_{5790}$ +149 (c, 0.8 $CHCl_3$).	Gram+, gram—, **Myco. smegmatis**
94	$C_{17}H_{14}O_4$ Canescin	**P. canescens**	Colourless needles (from EtOH) Monobasic acid 201-202 dec.		Fungi. Low antibacterial activity.
95*	$C_{17}H_{16}O_7$ Evernic acid	**Evernia prunastri**, **Usnea** sp., **Ramalina pollinaria**	Prisms Depside of orcinol group 169-70		**Myco. tuberculosis**
96	$C_{17}H_6O_7$ Antibiotic	**Monosporium bonorden**	Colourless cryst. 193·5	+203 ($CHCl_3$, 20°).	Fungi.
97*	$C_{17}H_{17}O_6Cl$ Griseofulvin	**P. griseofulvum**, other **Penicillium** spp.	Colourless, massive, rhombic or octahedral cryst. Neutral 218-221	286, 325 +370 (c, 2 $CHCl_3$, 17°); +337 (c, 1 C_3H_6O, 21°)	Fungi
98*	$C_{17}H_{18}O_6$ Dechlorogriseofulvin	**P. nigricans**	Needles Neutral 179-81	250, 286, 325 +390 (c,1C_3H_6O, 19°)	**Botrytis allii**
99*	$C_{17}H_{20}O_6$ Mycophenolic acid	**P. brevicompactum**, other **Penicillium** spp.	Colourless radiating needles Weak dibasic acid 141	Opt. inactive	Gram+, fungi

1	2	3	4	5	6
100	$C_{17}H_{23}NO_2$ Pyo II	**Pseudomonas aeruginosa**	Light yellow platelets 149-149.5	242, 330 (95% EtOH)	Gram+, gram— less sensitive
101*	$C_{17}H_{32}O_4$ Roccellic acid	**Roccella** spp., **Lecanora** spp.	Plates or leaflets Dibasic acid 130, 131		**Myco. tuberculosis t. bovinus**
102*	$C_{18}H_{12}N_2O_2$ Xanthocillin X	**P. notatum**	Yellow clusters of needles (from alcohol); yellow rhombic prisms (from ethyl acetate) Chars at 200		Gram+, gram—, **Myco. tuberculosis**
103*	$C_{18}H_{12}O_{10}$ Salazinic acid	**Parmelia** spp.	Needles Depsidone of β-orcinol group Darkens from 240 and carbonises at 260		**Staph. aureus**
104	$C_8H_4O_7$ Bostrycoidin	**Fusarium bostrycoides**	Brown or red laths in clusters. Substituted naphthoquinone pigment 243-44	251, 320	Gram+, **Myco. tuberculosis**
105*	$C_{18}H_{14}O_8$ Psoromic acid	**Psoroma crassum**, other lichen spp.	Needles. Depsidone of β-orcinol group 265		**Staph. aureus**
106*	$C_{18}H_{15}O_6Cl$ Pannarin	**Pannaria** spp.	Long prisms Depsidone of β-orcinol group 216-17		**Staph. aureus**
107*	$C_{18}H_{16}O_7$ Usnic acid	Lichen spp., fungal symbiont of lichen	Yellow cryst., form differs with solvent of crystallization 203-204 (d-form); 203 (l-form); 194 (dl-form).	226-230, 284 D-isomer: +445 to +515 (c, 2.0-3.19 $CHCl_3$, 20°) L-isomer: —445 to —478 (c, 2.0-3.08 $CHCl_3$, 20°)	Gram+, gram—, acid fast, fungi.
108	$C_{18}H_{16}O_8Cl_2$ Nordin	**P. paxilla** var. **echinulatum**	134-35. Contaminated with Estin has m.p. 214-16.		
109	$C_{18}H_{18}O_7$ Obtusatic acid	**Ramalina** spp.	Needles. Depside of orcinol group 208-209		**Staph. aureus**

1	2	3	4	5	6
110	$C_{18}H_{23}NO$ Pyo III	**Pseudomonas aeruginosa**	Colourless cryst. 2-(△′-nonenyl-)-4-quinolinol 151.5-153.5.	258, 266, 307, 338 (95% EtOH). 258, 267, 320 (ethanolic HCl); 260, 326 (ethanolic KOH)	
111	$C_{18}H_{25}NO$ Pyo Ic	**Pseudomonas aeruginosa**	2-Nonyl-4-quinolinol. 138.8-139.2.	236, 316, 328 (95% EtOH); 232, 300 (ethanolic HCl); 244, 314 (ethanolic KOH)	Gram,+ gram—
112	$C_{18}H_{32}O_2$ Linoleic acid	**P. crustosum**			Weak antibacterial activity.
113*	$C_{19}H_{14}O_4Cl_3$ Nidulin	**A. nidulans**	Colourless rhombs (from EtOH); shining slender rods (from petrol ether) 180	267, 323 inf. Opt. inactive ($CHCl_3$)	**Myco. tuberculosis**
114*	$C_{19}H_{14}O_5$ Vulpinic acid	**Evernia** spp. **Cetraria** spp.	Yellow prisms (from ether or EtOH); Yellow plates (from (from C_6H_6 or$CHCl_3$.) Aromatic acid. 148		**Myco. tuberculosis avium**
115*	$C_{19}H_{15}O_5Cl_3$ Nornidulin	**A. nidulans**	Heavy square plates (fraction I); rosettes of fine needles (fraction II); hexagonal plates or prisms (from petrol ether). 185-87 (fraction I); 214-16 (fraction II).	266, 323 inf.	Gram+, acid fast.
116	$C_{19}H_{16}O_6$ ∝-Viridin	**Trichoderma viride**	Colourless fine needles 208-17 dec.; 217-23 dec. (∝, β mixture)	241.3, 304.5 (alcohol) —213.4 ($CHCl_3$, 20°)	Fungi. Weak activity against protozoa
117	$C_{19}H_{16}O_6$ β-Viridin	**Trichoderma viride**	Fine needles. 140-dec. 217-23 dec. (∝, β mixture)	241.5, 304 (alcohol) —50.7 ($CHCl_3$, 20°) Viridins:—222 (c, 1 $CHCl_3$, 19°)	Fungi. Weak activity against protozoa
118*	$C_{19}H_{16}O_{11}$ Thamnolic acid	**Thamnolia vermicularis, Cladonia** spp., other lichen spp.	Faint yellow plates. Depside of β-orcinol group. 223 dec.		**Staph. aureus**
119*	$C_{19}H_{18}O_8$ Atranorin	**Evernia prunastri**, other lichen spp.	Colourless prisms. Depside of β-orcinol group. 196		**Staph. aureus**

1	2	3	4	5	6
120	$C_{19}H_{20}O_8$ Herquein	**P. herquei**	Yellow-brown cryst. 129 dec.		Gram+, gram—, **Myco. phlei**
121	$C_{19}H_{24}O_5$ Trichothecin	**Trichothecium roseum**	Colourless, slender, fibrous needles. Neutral ester. 118 cor.	220, 334 ($CHCl_3$ or hexane); 230, 325 (EtOH) +44 (c, 1.0 $CHCl_3$, 18°)	Fungi
122	$C_{19}H_{28}O_3$ Rosein II	**Trichothecium roseum**	Colourless fibrous needles. 186	+5.9 (c, 2 $CHCl_3$, 23°); $(\alpha)_{5461}$ +7.5 (c, 1 EtOH, 20°)	**B. subtilis, Myco. phlei**
123*	$C_{19}H_{32}O_4$ 1-Lichesterinic acid	**Cetraria** spp.	Needles. Monobasic lactonic acid. 124.		**Staph. aureus, Myco. tuberculosis avium**
124*	$C_{19}H_{32}O_4$ d-Protolichesterinic acid	**Cetraria islandica, Parmelia simodensis, Cladonia** spp.	Colourless, rhombic, leaflets with pearly lustre. Monobasic lactonic acid. 107·5.		**Staph. aureus**
125*	$C_{19}H_{32}O_4$ 1-Protolichesterinic acid	**Cetraria crispa**	Leaflets with pearly lustre. 106.		**Staph. aureus**
126*	$C_{20}H_{16}O_6$ Pinastric acid	**Cetraria** spp., **Lepraria flava f. quercina**	Orange needles. Related to phenylbenzoquinone pigment. 200-203.		**Staph. aureus**
	$C_{20}H_{17}O_5Cl_3$ Nidulin (See 113)				
127*	$C_{20}H_{22}O_5$ Pleurotin	**Pleurotus griseus**	Yellow, orange, amber needles. Neutral. 200-15 dec.	250. —20 (c. 0.59 $CHCl_3$, 23°)	Gram+, acid fast. Gram— less sensitive
128*	$C_{20}H_{22}O_7$ Diffractaic acid	**Usnea diffracta; Alectoria ochroleuca**	Needles. Depside of β-orcinol group. 189-90.		**Staph. aureus**
129*	$C_{20}H_{25}N_3O$ Prodigiosin	**Serratia marcescens**	Green, metallic leaflets; lustrous square pyramids; dark green with green reflex Monoacidic base. Red pigment. 151-52.	535-540 (acid-chloroform); base in EtOH: pH 7·4: 225.5, 288.5, 337, 471, 539; pH 11: 257, 281, 335.5, 468.5; pH 2.9: 216, 296, 371, 541 with inflec. at 275, 382, 510	Fungi and protozoa

1	2	3	4	5	6
130*	$C_{20}H_{26}O_8$ Rubrogliocladin	**Gliocladium roseum**	Dark red needles. Quinhydrone. 74.	275, 407	**Botrytis allii**; less active against **B. subtilis**; **E. coli**
131	$C_{20}H_{32}O_8$ Oregonensin	**Ganoderma oregonense**	White needles. Neutral. 82.	325 Opt. inactive	**M. pyogenes** var **aureus**, gram— and acid fast less sensitive
132	$C_{21}H_{18}O_6Cl_2$ Compound II	**A. nidulans**	214-16.		Gram+ cocci and Mycobacteria in synthetic media
133*	$C_{21}H_{23}O_5Cl$ Sclerotiorin	**P. sclerotiorum, P. multicolor**	Yellow cryst. Pigment. Azaphilone. 205-206.	+500 (c, 1 $CHCl_3$, 21°); $(\alpha)_{5790}$ +549 (21°)	Slight antibacterial activity
134*	$C_{21}H_{24}O_4$ Divaricatic acid $C_{21}H_{25}O_5Cl$ Sclerotiorin (See 133)	**Evernia** spp.	Needles. Depside of orcinol group. 137.		**Staph. aureus, Myco. tuberculosis avium**
135	$C_{21}H_{30}O_8$ Alternaric acid	**Alternaria solani**	Colourless, thin rectangular plates or elongated prisms. Unsaturated dibasic acid. 138.	273. Opt. inactive	Fungi
136*	$C_{21}H_{38}O_6$ Rangiformic acid	**Cladonia mitis, C. rangiformis**	Needles. Tribasic acid. 106.		**Staph. aureus**
137*	$C_{21}H_{38}O_7$ Caperatic acid	**Parmelia caperata, Nephromopsis** sp.	Leaflets. Tribasic acid. 132-133.5.		**Staph. aureus**
138*	$C_{22}H_{16}O_{12}$ Fumarprotocetraric acid	**Cetraria islandica, Cladonia** spp.	Small needles. Depsidone of β-orcinol group. 250-60.		**Staph. aureus**
139*	$C_{22}H_{26}O_5$ Didymic acid	**Cladonia** spp.	Needles. Dibenzofuran derivative. 172-73.		**Staph. aureus, Myco. tuberculosis avium**
140*	$C_{22}H_{26}O_8$ Sekikaic acid	**Ramalina** spp.	Needles. Depside of orcinol group. 147 dec.		**Staph. aureus, Myco. tuberculosis avium**

1	2	3	4	5	6
141*	$C_{22}H_{28}N_2O_5$ Mycelianamide	**P. griseofulvum**	Colourless shiny leaflets. Amide of o-mycelyl-N-pyruvyl-β-ketotyrosine. 170-72.	$(\alpha)_{5461}$:—217 (c, 0.8688 $CHCl_3$, 19°); $(\alpha)_{5790}$:–182 (c, 0·688 $CHCl_3$ 19°)	Gram+
142	$C_{22}H_{34}O_5$ Pleuromutilin (Drosophilin B)	**Pleurotus mutilis, Drosophila subatrata**	White cryst. 170-71.	290; end absorption below 230. +20 (c,3 absol. EtOH, 24°).	Gram+, **Myco. smegmatis**; less active against gram—. Influenza PR-8 virus in chick embryo
143*	$C_{22}H_{38}N_2O_6$ Enniatin B	**Fusarium orthoceras var enniatum**	173-76	—106 to —108 (c, 0·63 to 1.2 $CHCl_3$).	Mycobacteria, some fungi
144*	$C_{22}H_{38}O_6$ Ungulinic acid	**Polyporus benzoinus, P. betulinus**	Microcrystalline needles. Tribasic acid. 78-80.	Opt. inactive.	**M. pyogenes** var. **aureus.**
145*	$C_{23}H_{28}O_8$ Ramalinolic acid	**Ramalina** spp.	Prisms or plates. Depside of orcinol group. 163-64		**Staph. aureus**
146*	$C_{24}H_{30}O_7$ Anziaic acid	**Anzia** spp., **Cetraria sanguinea**	Minute needles. Depside of orcinol group. 124 dec.		**Staph. aureus**
147	$C_{28}H_{32}O_4$ Ophiobolin	**Ophiobolus miyabeanus**	White prisms. 181-82.		Fungi
148*	$C_{24}H_{42}N_2O_6$ Enniatin A	**Fusarium orthoceras** var **enniatum**	Colourless long needles. 121-22.	—90 to —92 (c, about 1 $CHCl_3$).	Gram+, acid fast, fungi
149	$C_{24}H_{42}N_2O_7$ Sambucinin	**Fusarium sambucinum**	Colourless plates or tetrahedra. Neutral 86-87.	Absorption below 219. —83.2 ±2 (c, 1 EtOH, 21°)	Gram+, **Myco. phlei**
150	$C_{24}H_{48}N_2O_6$ Baccatine A	**Gibberella baccata**	Colourless cryst. 135.		**M. pyogenes** var **aureus**, fungi.
151	$C_{25}H_{28}N_2O_6S_2$ Micrococcin	**Micrococcus** sp.	White, fine, long, silky needles in fans, sheaves or balls. 222-28 sinters.	345 with blue or purple fluorescence. +116 ±1 (EtOH, 21°)	Gram+, **Vibrio comma, Myco. tuberculosis**
152*	$C_{25}H_{28}O_8$ Lobaric acid	**Stereocaulon** spp., other lichen spp.	Needles. Depsidone or orcinol group 192.		**Staph. aureus**

1	2	3	4	5	6
153*	$C_{28}H_{32}O_7$ Perlatolic acid	**Cladonia** spp., **Parmelia** spp.	Needles. Depside of orcinol group. 108.		**Staph. aureus, Myco. tuberculosis avium**
154*	$C_{29}H_{32}O_8$ Boninic acid	**Ramalina boninensis**	Plates. Depside of orcinol group. 134.5.		**Staph. aureus**
155	$C_{25}H_{44}N_2O_7$ Avenacein	**Fusarium avenaceum**	Colourless plates or tetrahedra. Neutral. 139.	Absorption below 219. −101 ±2 (c, 1 EtOH, 19°).	Gram +, **Myco. phlei**
156*	$C_{29}H_{30}O_8$ Physodic acid	**Parmelia physodes, P. furfuracea**	Prisms. Depsidone of orcinol group. 205.		**Myco. tuberculosis**
157*	$C_{28}H_{32}O_8$ Olivetoric acid	**Parmelia olivetorum, Cornicularia** spp.	Needles. Depside of orcinol group. 151		**Staph. aureus, Myco. tuberculosis avium**
158*	$C_{28}H_{34}O_7$ Fumagillin	**A. fumigatus**	Colourless or light yellow cryst. Weak monobasic acid, monoester of decatetraenedioic acid. 189-94.	239, 304, 322, 336, 351. −26.6 (c, 0.25 MeOH, 25°); −24 (c, 5 $CHCl_3$, 25°).	Protozoa and viruses
159	$C_{29}H_{44-46}N_2O_7$ Fructigenin	**Fusarium fructigenum**	Colourless plates or tetrahedra. Neutral. 129.	Absorption below 219. −103 ±2 (c, 1 EtOH, 18°).	Gram+, **Myco. phlei**
160	$C_{28}H_{46}N_2O_7$ Lateritiin II	**Fusarium lateritium**	Colourless plates or tetrahedra. Neutral. 125.	Absorption below 219. −92±1.6 (c, 1.2 EtOH, 19°).	Gram + **Myco. phlei**
161	$C_{29}H_{40}O_7$ Bongkrekic acid	**Pseudomonas cocovenans**	Amorphous.	239, 263 (0.01% $NaHCO_3$); 238, 267 (EtOH). +165 (2% $NaHCO_3$, 22°); +105 (96% EtOH, 22°).	Gram+, gram—, fungi.
162	$C_{30}H_{22}O_{10}$ Rugulosin	**P. rugulosum, P. wortmanni**	Yellow cubes or prisms (from EtOH or acetone). Related to polyhydroxyanthroquinones. 293 dec.	$(\alpha)_{5461}^{18}$ +605 (dioxane; falls to +222 on exposure to light for periods of 14 days or more).	Gram+, gram—, **Myco, smegmatis, Pythium intermedium**

1	2	3	4	5	6
163*	$C_{30}H_{52}O_2$ Zeorin	**Anaptychia** spp., other lichen spp.	Colourless hexagonal plates. Triterpenoid acid. 253.		**Staph. aureus**
164*	$C_{31}H_{46}O_4$ Polyporenic acid C	**Polyporus benzoinus, P. betulinus**	Microcrystals. Triterpenoid acid. 285-90 dec.	$(\alpha)^{20}_{5461}$ +8.19 (c, 5.1 pyridine).	Acid fast. Slight activity against **M. pyogenes** var. **aureus** and **E. coli**
165*	$C_{32}H_{42}O_8$ Helvolic acid	**A. fumigatus**	White, long, fine needles. Monobasic acid. 211.3-212.1; 220-26	230, 234, 231, 322. —113 (c, 3.1 $CHCl_3$, 23°); —117 (c, 2.6 $CHCl_3$, 23°); —124 (c, 1 $CHCl_3$, 25°)	Gram + gram—, acid fast, fungi.
166	$C_{32}H_{48}O_8$ Cephalosporin P_1	**Cephalosporium** sp.	Needles. Acidic. Polycyclic aromatic structure. 147.	211—218. +28.	Gram+, **Myco. phlei**
167*	$C_{32}H_{60}O_{14}$ Glyco-lipidic antibiotic	**Pseudomonas aeruginosa**	Colourless, thin, rectangular platelets. 86.	—84 (c, 3 $CHCl_3$)	**Myco. tuberculosis** var. **hominis**.
168*	$C_{35}H_{23\text{-}25}N_5O_6$ Violacein	**Chromobacterium violaceum**	Violet black microcryst. Thick needles. Elongated, rectangular cryst. Violet pigment. Above 350 dec.		Gram+, **Neisseria meningitis**, fungi, protozoa
169	$C_{37}H_{62\text{-}66}O_7$ Ustilagic acid	**Ustilago zeae**	Colourless, needle-like cryst. Mixture of closely-related partially acylated glucolipids. 141-47.	+7 (c, 1 pyridine, 23°).	Gram, +gram—, fungi, Actinomycetes
170	$(C_{39}H_{74}N_{12}O_9)n$ Circulin	**Bacillus circulans**	White amorphous solid (sulphate). Basic polypeptide. Sulphate: 226-28; HCl: 232-36 dec.	None significant. Sulfate: —61.6 (c, 1.25 water, 25°); HCl: —60.1 (c, 2.094 water, 25°)	Gram—. Less active against gram+, **Trichomonas vaginalis**, fungi.
	$C_{42}H_{28\text{-}30}N_6O_7$ Violacein (**See** 168)				
171	$C_{48}H_{60}O_{16}$ Glutinosin	**Myrothecium verrucaria**	Colourless thin plates. Darkens, but no melting by 300.	About + 54 (c, 0.2 C_6H_6, 20°).	Fungi

1	2	3	4	5	6
172	$C_{50}H_{97}N_{15}O_{15}$. Cl_4 Polymyxin D (4 HCl)	**Bacillus polymyxa**	No definite structure; birefringent. Basic polypeptide. 228-35 dec. (for Polymyxins)	No characteristic spectrum.	Gram—
173	$C_{56}H_{96}N_{12}O_{13}$ Polypeptin	**Bacillus krzemieniewski**	Cryst. form varies with solvent; triangular prisms from 65% EtOH. Basic polypeptide. 176.	252, 258, 264. —93.3 (isopropyl alcohol, 20°).	Gram+, gram—, **Myco. tuberculosis**, fungi.
174	$C_{56}H_{104}N_{16}O_{14}$. Cl_5 Polymixin B_1 (5 HCl)	**Bacillus polymyxa**	No definite structure; birefringent. Basic polypeptide. 228-35 dec. (for Polymyxins).	No characteristic spectrum. —85.1 (c, 2.33 in 75% EtOH, 25°)	Gram—
175*	$C_{60}H_{92}N_{12}O_{10}$ Gramicidin S	**Bacillus brevis**	Thin, colourless needles. Cyclic decapeptide. 245-47, 256-58, 268-70.	—292 (c, 1.5 EtOH, 18°); —295 (c, 1.5 EtOH, 20°).	Gram+, gram—
176*	$C_{66}H_{86}N_{13}O_{13}$ Tyrocidine A	**Bacillus brevis**	Colourless, fine needles or rods (HCl). Basic polypeptide. 240-42.	290. —111 (c, 1.37 in 50% EtOH 25°).	Gram+, Actinomycetes; less active against gram—, protozoa.
177*	$C_{66}H_{97}N_{15}O_{17}S$ Bacitracin F	**Bacillus subtilis; B. licheniformis.** Conversion of Bacitracin A	White, amorphous powder. Weakly basic polypeptide.	290.	
178*	$C_{66}H_{103}N_{17}O_{16}S$ Bacitracin A	**Bacillus subtilis; B. licheniformis**	White, hygroscopic, amorphous powder. Weakly basic polypeptide.	253. —3.6 (c, 5.0 in 0.01 HAc, 25°).	Gram+
179*	$C_{68}H_{88}N_{14}O_{13}$ Tyrocidine B	**Bacillus brevis**	Colourless needles or rods (HCl). Basic polypeptide.		As for Tyrocidine A (176).
180	$C_{71}H_{112\text{-}114}N_{18}O_{17\text{-}18}S$ Bacitracin B	**Bacillus subtilis**	White, highly hygroscopic amorphous powder Weakly basic polypeptide	253. —2.8 (c, 5.0 in 0.01 HAc, 25°).	Gram+
181	$C_{127}H_{166}N_{26}O_{26}$ Tyrocidine (mixture)	**Bacillus brevis**	HCl: Colourless fine needles or rods. Mixture of basic polypeptides. 237-39 uncor., 240 cor., dec.	—101, —102 (c, 1 in 95% alcohol, 25°).	Gram+, **Actinomyces spp.**, less active against gram—

1	2	3	4	5	6
182	$C_{148}H_{210}N_{30}O_{26}$ Gramicidin	**Bacillus brevis**	Colourless platelets with pointed or rectangular ends. Natural polypeptide, a component of Tyrothricin. 228-31.	281.5, 290.5, 271. +3 (c, 0.17 in 95% EtOH, 20°)	Gram+, protozoa
		ANTIBIOTICS FOR WHICH EMPIRICAL FORMULA IS NOT KNOWN			
183	Xerosin	**Achromobacter xerosis**	Acid precipitable material.	255-260 (aq. soln.)	In vivo activity in mice infected with influenza A and B viruses, Newcastle disease, mouse pneumonitis
184	Alternarine	**Alternaria solani**	White needles. 230.		Gram+, gram—, acid fast, fungi.
185	Gigantin	**Aspergillus terreus** var. **antibioticus**	110.		**E. coli**
186	A. U. N. I	**Aspergillus nidulans**	Neutral. 155-56.		Gram+ cocci and Mycobacteria.
187	A. U. N. II	**Aspergillus nidulans**	Neutral. c. 270 dec.		Similar to A. U. N. I (186)
188	A. U. N. III	**Aspergillus nidulans**	Neutral. 225.5—226.5.		
189	Terrecin	**Aspergillus terreus**	Light yellow prisms. 219-20.		Gram+, less active against gram—
190	Brevolin	**Bacillus brevis**	HCl: Yellowish-white, amorphous.	272.5 (99% MeOH). —18.9 (c, 1 MeOH, 26°)	Gram+, some gram—, acid fast
191	Gramicidin A	**Bacillus brevis**	Neutral polypeptide. 227-228.		Gram+, protozoa
192	Gramicidin B	**Bacillus brevis**	Neutral polypeptide. 258-59.		Gram,+, protozoa
193	Gramicidin C	**Bacillus brevis**	281.		Gram+, gram—
194	Lichenformins A, B, C	**Bacillus licheniformis**	HCl: White, amorphous powder. Char on heating. Peptides.	Below 250 (impurities affect u. v. absorption). HCl: A: -37.4; B:—37.7; C:—36.8.	Gram+, gram—. **Myco. phlei** inhibited at higher concn.

1	2	3	4	5	6
195	Esperin	**Bacillus mesentericus**	Na salt : Needles. 195; Na salt: 268-69 dec.		**Myco. tuberculosis**
196	Pumilin	**Bacillus subtilis**	Lemon yellow, small hexagonal crystals. Largely non-peptide. Does not melt below 360.	365, 378, 400.	Gram+
197	Bacillomycin	**Bacillus subtilis**	Colourless, microscopic needles or rosettes. Polypeptide with titratable acid function.	277 (n-butanol-water-acetic acid-95% ethanol) 296 (alcoholic NaOH) Opt. inactive(EtOH)'	Gram+, Gram— at higher concn.
198	Bacitracin C	**Bacillus subtilis**	White, hygroscopic, amorphous powder. Weakly basic polypeptide.	250, 268.	
199	Bacitracins D, E	**Bacillus subtilis**	White, hygroscopic, amorphous. powder. Weakly basic polypeptide.	253.	
200	Bacitracins F_1, F_2, F_3	**Bacillus subtilis**		253, 288.	
201	Bacitracin G	**Bacillus subtilis**		250, 268.	
202	Iturin L	**Bacillus subtilis**	Grey powder. Protein.	278.	Gram+, **P. notatum**
203	Iturin N	**Bacillus subtilis**	Yellow powder.	270.	
204	Iturin O	**Bacillus subtilis**	Brown substance.	260.	
205	Subtenolin	**Bacillus subtilis**	Light yellow powder, somewhat hygroscopic.	End absorption, 270.	Gram+, some gram—
206	Rhizobacidin	**Bacillus subtilis**	Crystalline. Peptide. 215-20.		Rhizobium
207	Cephalosporin P_2	**Cephalosporium** sp.	White, greasy, amorphous solid. Acidic. 151.	211.	
208	Cephalosporin P_4	**Cephalosporium** sp.	Light fawn coloured cryst. Acidic. 220-30.	211.	

1	2	3	4	5	6
209	Cephalothecin	**Cephalothecium sp.**	124-26 dec.		Fungi.
210	Clitocybins	**Clitocybe candida**	Colourless, long orthorhobic cryst. 77.		Gram+, gram—. **Myco. tuberculosis**
211	Diatretyne 3	**Clitocybe diatreta**		253, 280, 297, 316, 339.	
212	Quadrifidin B_2	**Coprinus quadrifidus**	White crystals turning black Neutral.	274 (ether).	Gram+, gram—, **Myco. tuberculosis**
213	Quadrifidin B_3	**Coprinus quadrifidus**	Strongly dichroic white cryst. Neutral.	265, 276, 294, 313 (ether).	Gram+, gram—, **Myco. phlei.**
214	Drosophilin D	**Drosophila subatrata**		217, 259, 274, 290, 309 (EtOH).	**M. pyogenes** var. **aureus, B. subtilis.**
215	Drosophilin C	**Drosophila subatrata**	Polyacetylene.	238, 251, 265, 280 (ether).	Gram+, gram—, **Myco. smegmatis**
216	Coliformin	**Escherichia coli**	Polypeptide.	272 broad band.	Fungi and yeast
217	Fuligolic acids	**Fuligo septica**	I Amorphous black pigment. II Yellow pigment. I does not melt or sublime below 360.		**W. perfringens**
218	Oxysporin	**Fusarium oxysporum**	c. 70.		**M. tuberculosis** var. **hominis**
219	Lenzitin	**Lenzites sepiaria**	Colourless thin needles. 166-68.		Gram+, gram—
220	Ramycin	**Mucor ramannianus**	Colourless orthorhombic plates. 158-60 dec.	No specific absorption	Gram+, **Myco. tuberculosis H37Rv**
221	Factor	**Penicillium albidum**	Colourless cryst. 156 dec		Fungi. Weak activity against bacteria
222	Factor	**Penicillium herquei**	Yellow and brownish rectangular rods. Above 250 dec.		**Staph. aureus** and **Shigella shigae**
223	Notatin	**P. notatum**, other **Penicillium** spp.	Yellow or buff-coloured powder. Flavoprotein, glucose-oxidase enzyme.	270-280, 375-380, 450-460 —4.8 (c, 0.012 water, 32°)	Gram+, Gram—,

1	2	3	4	5	6
224	Factor	**P. spinulosum**	White, fine needles. 183-85.		Grant+, gram—
225	Wortmannin	**P. wortmanni**	Colourless solid. Neutral 240 dec.		Specific against **Botrytis allii, B. cinerea, B. fabae, Gladosporium herbarum, Rhizopus stolonifer.**
226	Biformyne 1	**Polyporus biformis**	Polyacetylene.	259, 274, 291, 310.	Gram+, gram−, acid fast, fungi.
227	Biformyne 2	**Polyporus biformis**	Polyacetylene.	263, 274, 290, 310.	Similar to that of Bifromyne 1 (226)
228	Comirin	**Pseudomonas antimycetica, Bacterium antimyceticum**	Whitish amorphous powder Peptide containing an ether soluble moiety. 230-35 dec. depending on rate of heating.		Fungi and yeast
229*	Viscosin	**Pseudomonas viscosa**	Acidic polypeptide. 269 dec., 270-73 dec.	—162.2 (20°), 168.3 (29°)	**Myco. tuberculosis**
230	Marcescin	**Serratia marcescens**	Polypeptide.	240, 260.	Gram+, gram—, **Myco. tuberculosis**
231	Sphaerophorin	**Sphaerophorus compressus**	140.		**M. pyogenes** var. **aureus**
232	Nisins A, B, C, D	**Streptococcus cremoris, Streptococcus lactis**	Nearly white needles. Low molecular weight protein or polypeptide.	275.	Gram+, gram—, **Myco. tuberculosis, Actinomyces.**

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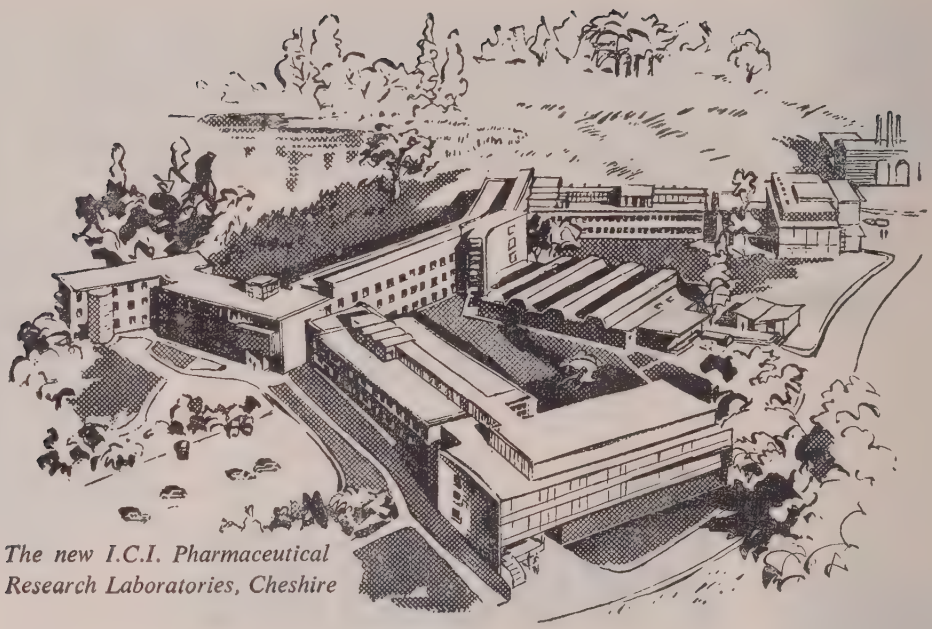

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The Priceless Ingredient

In the city of Bagdad lived Hakeem, the Wise One, and many people went to him for counsel, which he gave freely to all, asking nothing in return.

There came to him a young man, who had spent much but got little, and said: "Tell me, Wise One, what shall I do to receive the most for that which I spend?"

Hakeem answered: "A thing that is bought or sold has no value unless it contains that which cannot be bought or sold. Look for the Priceless Ingredient."

"But, what is this Priceless Ingredient?" asked the young man.

Spoke then the Wise One: "My son, the Priceless Ingredient of every product in the market-place is the Honor and Integrity of him who makes it. Consider his name before you buy."

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